16.1 Study Information

16.1.1 Protocol and Amendments

COVANCE.
THE DEVELOPMENT SERVICES COMPANY

FINAL RESEARCH PROTOCOL
AMENDMENT NO. 1

A SINGLE-CENTER, PILOT EXPLORATORY STUDY TO EVALUATE STUDY DESIGN, STUDY LOGISTICS, AND BIOANALYTICAL METHODS TO MEASURE SMOKE EXPOSURE IN ADULT SMOKERS OF 3.0 TO 6.9 MG FTC TAR DELIVERY CIGARETTES AS COMPARED TO ADULT NON-SMOKERS (PILOT TOTAL EXPOSURE STUDY)

Protocol No. PM-8450

PM Project No. 1148
Covance CRU Study No. 12226-8450

for

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STUDY IDENTIFICATION

A SINGLE-CENTER, PILOT EXPLORATORY STUDY TO EVALUATE STUDY DESIGN, STUDY LOGISTICS, AND BIOANALYTICAL METHODS TO MEASURE SMOKE EXPOSURE IN ADULT SMOKERS OF 3.0 TO 6.9 MG FTC TAR DELIVERY CIGARETTES AS COMPARED TO ADULT NON-SMOKERS (PILOT TOTAL EXPOSURE STUDY)

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ABBREVIATIONS

ABP Hb	= Hemoglobin adducts of aminobiphenyl
abs	= Absolute
ALT	= Alanine Aminotransferase
Anti-HCV	= Hepatitis C Virus antibody
AST	= Aspartate Aminotransferase
BUN	= Urea Nitrogen (serum)
°C	= Degrees Celsius
CAP	= College of American Pathologists
CBC	= Complete Blood Count
CFR	= Code of Federal Regulations
CLIA	= Clinical Laboratory Improvement Amendments
CO	= Carbon monoxide
CRF	= Case Report Form
CRU	= Clinical Research Unit
dL	= Deciliter
ECG	= Electrocardiogram
Ed	= Editor
e.g.	= For example (Latin: *exempli gratia*)
et al.	= And others (Latin: *et alii*)
etc.	= And so forth (Latin: *et cetera*)
ETS	= Environmental tobacco smoke
Ext.	= Extension
°F	= Degrees Fahrenheit
FDA	= Food and Drug Administration
FEV1	= Forced expiratory volume in one second
FTC	= Federal Trade Commission
FVC	= Forced vital capacity
GC	= Gas chromatograph
GC-NPD	= Gas chromatograph with nitrogen/phosphorus detector
GCP	= Good Clinical Practice
GGT	= Gamma Glutamyl Transferase
HbsAg	= Hepatitis B Surface Antigen
HDL	= High density lipoprotein
HDPE	= High density polyethylene

ABBREVIATIONS

HDYF?	= How do you feel? Inquiry
Hep	= Hepatitis
HIV	= Human Immunodeficiency Virus
HPF	= High Power Field
HPLC	= High performance liquid chromatograph
Hr	= Hour
ICH	= International Conference on Harmonization
i.e.	= That is to say (Latin: *id est*)
Inc.	= Incorporated
IRB	= Institutional Review Board
K_3EDTA	= Potassium (as trivalent ion) Ethylenediaminetetraacetate
LC/MS/MS	= Liquid chromatography with tandem mass spectroscopy detector
LDH	= Lactate Dehydrogenase
LDL	= Low density lipoprotein
Ltd.	= Limited
MCH	= Mean Cell Hemoglobin
MCHC	= Mean Cell Hemoglobin Concentration
MCV	= Mean Cell Volume
MD	= Medical Doctor (Professional Degree)
ME	= Maine
mg	= Milligram
mL	= Milliliter
MS	= mass spectrometry
NNAL	= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNAL-gluc	= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol glucuronide
NNK	= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
No	= Number (also designated as N)
PR	= Interval from end of the P wave to the onset of the QRS complex
PTR-MS	= Proton transfer reaction mass spectrometry
RBC	= Red blood cell
QRS	= QRS complex duration (measured from its onset to ST segment onset)
QTc	= Interval from onset of QRS complex to end of T-wave, corrected for rate
Ref	= Reference
SGOT	= Serum Glutamic-Oxaloacetic Transaminase

ABBREVIATIONS

SGPT	= Serum Glutamic-Pyruvic Transaminase
SST	= Serum Separator Tube
TEA	= Thermal energy analyzer
TES	= Total Exposure Study
UA	= Urinalysis
U.S.A.	= United States of America
UV	= Ultraviolet
WBC	= White Blood Cell Count
%COHb	= Percent carboxyhemoglobin
8-epi-$PGF_{2\alpha}$	= 8-epi-prostaglandin $F_{2\alpha}$

1. SUMMARY

Title: A Single-Center, Pilot Exploratory Study to Evaluate Study Design, Study Logistics, and Bioanalytical Methods to Measure Smoke Exposure in Adult Smokers of 3.0 to 6.9 mg FTC Tar Delivery Cigarettes as Compared to Adult Non-Smokers (Pilot Total Exposure Study)

Objectives:

- To establish the validity of the design concepts (e.g., sample collection, feasibility, and precision of analytical methods for biomarkers, sample handling and stability, data acquisition by questionnaire) to be used in a subsequent large study of adult smokers representing all tar and nicotine categories in the U.S. market.
- In particular, the study should determine
  - The intra- and inter-individual variability of each estimate of biomarkers of exposure and biomarkers of effect.
  - If the selected biomarkers of exposure and effect can differentiate between adult smokers of 3.0 to 6.9 mg tar (FTC) cigarettes and adult non-smokers.

Study Design: This study employs a single-center, out-patient visit design. It is an exploratory observational study with 2 parallel groups (adult smokers and adult non-smokers) and 2 subgroups (male and female) within each group.

Recruitment: Subjects will be recruited from the geographic area of the research site using appropriate advertising (e.g., newspaper and flyers). As an initial part of the recruitment process, the interested people will be asked a series of questions via a telephone screen to evaluate their suitability for the study population prior to inviting them to the research site for a screening visit.

Study Population: The study population will consist of approximately 135 healthy, adult male and female subjects, 21 years of age or older. This population will include a distribution of approximately 70 smokers (distributed approximately equally between adult male and female smokers) and approximately 65 adult non-smokers (distributed approximately equally between adult non-smoking males and females). Subject smoking status will be defined by cigarette consumption of a minimum of 1 cigarette per day over the last 12-month period (Ref. 1).

Site Visits: The subjects will report to the study site for a Screening visit within 28 days prior to entry in the actual study. After Enrollment, the subjects will visit the study site 4 times (i.e., once during each Week 1, 2, 3, and 6). The subjects will receive the necessary supplies at each visit to collect the needed samples/information for the next scheduled visit. The visits will be scheduled such that the blood samples for analysis of biomarkers will be conducted on 2 of their leisure days and 2 of their non-leisure days. The 24-hour urine collections will be conducted on 2 non-leisure days and 1 leisure day.

Collections:

Exhalate: Samples of subject exhalate for determination of acetonitrile will be collected at site visits during Weeks 1, 3, and 6. Levels of carbon monoxide in exhalate will be determined at site visits during Weeks 1, 2, 3, and 6. The collection/determination times will occur before any other procedures occur and will be within 30 minutes of arrival at the study site.

Blood: Blood samples for determination of acetonitrile and carboxyhemoglobin in blood will be collected at site visits during Weeks 1, 2, 3, and 6. Blood samples for determination of hemoglobin adducts in RBCs will be collected at site visits during Weeks 1 and 6. Blood samples for determinations of malondialdehyde and fibrinogen in plasma, and HDL-cholesterol, LDL-cholesterol, and C-reactive protein in serum will be collected at site visits during Weeks 1, 3, and 6, as outlined in Table 1. Blood collections for screens of HIV and hepatitis antibodies in serum will be collected at site visits during Weeks 1, 2, 3, and 6. Collection of blood samples will occur after the exhalate collection and within 30 minutes of arrival at the study site.

Urine: Subjects will be instructed to collect urine samples as follows: a void upon waking during Weeks 1, 2, and 3 will be collected separately into a smaller collection container, frozen, and used for analysis of 11-dehydro-thromboxane B_2 and 8-epi-$PGF_{2\alpha}$ (and spot analyses of urinary creatinine). After that void, the subject will be instructed to collect all other voids into a urine collection device, combine them in a large storage container, and store the large urine collection container under refrigerated conditions (an insulated type box/cooler will be provided by the research site along with gel pack refrigerants for this purpose). The 24-hour urine samples collected during Weeks 1, 2, and 3 will be analyzed for malondialdehyde, nicotine and nicotine metabolites, and creatinine. The 24-hour urine samples collected during Weeks 1 and 3 will also be analyzed for NNAL and NNAL-glucuronide.

Sputum: The subjects will be given a separate collection container for at-home collection of spontaneous sputum on the day of a scheduled visit to the research site. Additionally, spontaneous sputum samples will be collected at each visit (if samples are produced). The samples will be maintained in a frozen state until the end of the study duration, at which time they may be processed and analyzed further.

Diary: Each subject will be asked to keep a diary of exposure to other people's tobacco smoke and/or smoking consumption from the time of 48 hours prior to the urine collection and during each 24-hour urine collection interval (i.e., until they arrive at the study site).

Interviews/ Questionnaires/ Surveys: Potential subjects will undergo a telephone screening during which the subject's eligibility for the study will be preliminarily determined. If the potential subject satisfactorily completes the telephone screen and reports to the site for a screening visit, a screening interview will be conducted to determine the ongoing eligibility of the potential subject (e.g., health/medical history, concomitant medications, tobacco use history, and intercurrent illnesses that may be of importance during the study).

Interviews/ Questionnaires/ Surveys:	During the enrollment visit and again at Week 6, a full questionnaire will be administered by a trained interviewer during which the subject will be asked about demographics, exposures (i.e., occupational, hobbies, household, solvents), exposure to other people's tobacco smoke, home heating/ ventilation systems, dietary characteristics, use of non-tobacco nicotine products, and physical activity for all subjects. Smoking behaviors/ consumption for smokers will also be investigated. In addition, at each site visit during Weeks 1, 2, 3, and 6, the subjects will be asked a series of questions (i.e., Weekly Survey) related to the smoking behaviors/consumption and exposure to other people's tobacco smoke over the 3 days prior to the site visit.
Lab Safety Tests:	Complete laboratory evaluations (chemistry [fasted for a minimum of 6 hours], hematology [CBC], and complete urinalysis [UA]) will be collected at Screening and at Enrollment. For female subjects of childbearing potential, a urine sample will be collected at each clinic visit for pregnancy testing at the research site. Postmenopausal (amenorrheic for a period of 1 year or more) or surgically sterile females will not be required to undergo a pregnancy test. If a subject tests positive for a pregnancy, she will immediately be discontinued from the study, informed of the risks of her behaviors to the unborn fetus (i.e., smoking and/or drinking), and referred to her primary care provider.
Lung Function Tests	At the Screening visit, each subject will undergo pulmonary function tests to determine the FVC and FEV1. If the subject's level is less than 75% of the expected value, the subject will be unable to participate in the study.
Other Lab Tests:	Hepatitis panel (including HBsAg and anti-HCV) and HIV antibody screens will be performed at every visit. A urine drug screen for selected illicit drugs (not including alcohol) will be performed at Screening and repeated at Enrollment. At the time of Enrollment, a urine sample will be collected 4 to 5 hours after challenge with caffeine to determine the CYP1A2 and NAT2 phenotype of the subjects.

12-lead ECG:	A 12-lead ECG will be obtained at Screening.
Vital Signs:	Vital signs (oral temperature, respirations, and automated seated blood pressure and pulse) will be obtained at Screening, at Enrollment, and at each study site visit. Vital signs will be measured after the subjects have been seated for a minimum of 5 minutes.
Physical Exam:	A physical examination will be performed at Enrollment.
HDYF? Inquiry:	Subjects will be asked a non-leading How Do You Feel? (HDYF?) question, such as "Have there been any changes in your health status since you were last seen?" at each post-Screening study site visit. Any changes in the subject's health status will be recorded as an intercurrent illness. This inquiry will include questions about any concomitant medications that the subject may be using.

Table 1 - Study Flow Chart

Study Procedures	Screen[1]	Enrollment	Week 1*	Week 2*	Week 3*	Week 4*	Week 5*	Week 6*
Medical History	X	X[2]						
Physical Exam		X						
12-Lead ECG	X							
Lung Function Tests[3]	X							
Vital Signs[4]	X	X	X	X	X			X
HDYF? Inquiry[5]		X	X	X	X			X
Concomitant Medications[6]	X	X	X	X	X			X
Weekly Survey[4]			X	X	X			X
Complete Questionnaire[8]		X						X
Blood Sampling[9]								
Acetonitrile (Blood)			X	X	X			X
Carboxyhemoglobin (Blood)			X	X	X			X
Hemoglobin adducts (RBCs)			X					X
HDL-cholesterol and LDL-cholesterol (Serum)			X		X			X
Malondialdehyde (Plasma)			X		X			X
Fibrinogen (Plasma)			X		X			X
C-Reactive Protein (Serum)			X		X			X
Urine Sampling[9]								
Malondialdehyde			X	X	X			
Nicotine and Nicotine Metabolites[8]			X	X	X			
NNAL and NNAL-glucuronide[8]			X		X			
Creatinine			X	X	X			
11-Dehydro-thromboxane B_2[9]			X	X	X			
8-Epi- $PGF_{2\alpha}$[9]			X	X	X			
Exhalate Sampling[10]								
Acetonitrile			X		X			X
Carbon Monoxide			X	X	X			X
Spontaneous Sputum Sampling[7]		X	X	X	X			X
Diary Record[4]			X	X	X			X
Cigarette Collection[7]			X	X	X			X
Cigarette Pack Collection[8]			X	X	X			X
Urine Pregnancy Test[1]	X	X	X	X	X			X
Chem, CBC & UA (fasted)[1]	X	X						
CYP1A2 and NAT2 Phenotyping[1]		X						
Hep & HIV Screen	X	X	X	X	X			X
Urine Drug Screen[8]	X	X						

*Visit schedules will be made to accommodate the subject's schedule as much as it can. However, visits will be arranged such that a subject will complete the sample (blood) collections on 2 of his/her leisure days and 2 of his/her non-leisure days. The urine collections will be scheduled such that 2 collections will be conducted on the subject's non-leisure days and 1 collection will be conducted on the subject's leisure day. If a subject is unable to visit the site during Weeks 1, 2, or 3, the visit may be done during Weeks 4 or 5. For the Week 6 visit, there is a 7-day window for the visit (i.e., Week 6 ± 7 days).

[a]Subjects will undergo a telephone screen prior to visiting the site for the Screening visit. The telephone screen will allow for the initial eligibility of the potential subject to be determined.

[b]Interim medical history only to determine intercurrent illnesses at time of enrollment.

[c]Lung function tests will consist of FVC and FEV1 only and must be >75% of expected to be included in the study.

[d]Vital signs (including oral temperature, respiratory rate, automated seated blood pressure and pulse) obtained at Screening, Enrollment, and at each site visit where a blood and/or urine sample is obtained.

[e]How Do You Feel? inquiries will be performed at each post-Screening vital signs measurement. Any reported findings will be recorded as an intercurrent illness/physical finding.

[f]Any medications being taken by a subject and the reason for its use will be documented during each site visit.

[g]Weekly surveys will be administered at the time the subject reports to the research site during Weeks 1, 2, 3, and 6. These surveys will include questions regarding the activities within the last 8 to 10 hours, smoking status and/or exposure, and any changes in the subject's overall status since the last visit.

[h]Full questionnaires will be conducted at the Enrollment visit and at Week 6 to assess smoking behaviors and exposure (household, occupational, and casual [i.e., hobbies]), demographics, dietary characteristics, and overall status of the subjects. A trained interviewer at the study site will administer the questionnaire.

[i]Blood samples will be collected for determination of acetonitrile and carboxyhemoglobin in whole blood at site visits during Weeks 1, 2, 3, and 6. Blood samples for the determination of hemoglobin adducts of 3- and 4-aminobiphenyl in RBCs will be collected at site visits during Weeks 1 and 6. Blood samples for determinations of HDL-cholesterol and LDL-cholesterol, malondialdehyde, fibrinogen, and C-reactive protein in plasma or serum will be collected at site visits during Weeks 1, 3, and 6.

[j]Subjects will be instructed to complete urine collections during the 24-hour interval prior to site visits for Weeks 1, 2, and 3. For each subject, 2 collections will be scheduled on non-leisure days and 1 collection will be scheduled on a leisure day. Samples collected during Weeks 1, 2, and 3 will be analyzed for malondialdehyde, nicotine and nicotine metabolites, and creatinine. The samples collected during Weeks 1 and 3 will also be analyzed for NNAL and NNAL-glucuronide.

[k]Results from these analyses will be reported as mass/24-hours, mol/24-hours, mass/mg creatinine, and mol/mg creatinine.

[l]Urine samples for 8-epi-$PGF_{2\alpha}$ and 11-dehydro-thromboxane B_2 will be collected as an early morning void on the days that the 24-hour urine samples are collected. Additionally, creatinine will also be analyzed in these samples so that they can be reported as mass/mg creatinine and mol/mg creatinine.

[m]Exhalate samples for determination of acetonitrile will be collected into special Tedlar bags at site visits during Weeks 1, 3, and 6. Carbon monoxide in exhalate measurements will be performed at the research site during Weeks 1, 2, 3, and 6. Collections/measurements will occur within 30 minutes of arrival at the research site.

[n]Spontaneous sputum samples, if any are produced by the subjects, will be collected on the morning of site visits for Weeks 1, 2, and 3, and during other site visits (i.e., enrollment and Week 6) as appropriate.

[o]Subjects will be instructed to record smoking consumption and/or exposure to other people's smoke in a diary during a 72-hour interval prior to site visit during Weeks 1, 2, 3, and 6.

[p]Smoking subjects will be instructed to collect filters/butts of cigarettes smoked during the interval of the 72-hour diary recording interval during Weeks 1, 2, 3, and 6. The number of butts collected and the number recorded in the diary will be compared against each other. Any discrepancies will be noted.

[q]Smoking subjects will be instructed to collect all packs from which a cigarette was removed during the 72-hour interval prior to site visit (i.e., during diary recording period) during Weeks 1, 2, 3, and 6.

[r]Urine samples will be collected from female subjects of child-bearing potential at each site visit for pregnancy testing (pregnancy testing will be performed at the research site).

[s]Blood samples (after a minimum 6 hour fast) for chemistry and hematology, and urine sample for urinalysis collected at Screening and Enrollment.

[t]Urine samples will be collected 4 to 5 hours after challenge with caffeine for CYP1A2 and NAT2 phenotyping of subjects.

[u]Urine drug screen does not include alcohol.

2. INTRODUCTION AND BACKGROUND

2.1 Introduction

The overwhelming medical and scientific consensus is that cigarette smoking causes lung cancer, heart disease, emphysema, and other serious diseases in smokers. Smokers are far more likely to develop serious diseases, like lung cancer, than are non-smokers. Not only is the relationship between specific smoke constituents and these disease states not well understood, the amount of smoke and smoke constituents to which a smoker is exposed is also not well-defined. Studies suggest that machine-derived smoke composition data are not suitable measures of smoker exposure to smoke constituents. To determine the exposure of adult smokers to cigarette smoke in the U.S., a more direct evaluation of the levels of smoke constituents or their metabolites in appropriate biofluids has been proposed. This investigation will include evaluation of biomarkers of exposure and biomarkers of effect[1] in adult smokers who regularly smoke brands of 3.0 to 6.9 mg tar yield, as measured by the Federal Trade Commission (FTC) methods, and published periodically by the Tobacco Institute Testing Laboratory.

Criteria for selection of the biomarkers of exposure for study were based on National Research Council guidelines for validating markers for environmental tobacco smoke (ETS), with modifications described in a 1997 U.S. Occupational Safety and Health Administration workshop on assessment of workplace exposure to ETS (Benowitz, 1999, Ref. 2). The criteria employed for these selections were:

- Unique or nearly unique to tobacco smoke.
- Representative of particulate and gas phase tobacco smoke.
- Representative of health-relevant tobacco smoke constituents.
- Constituent metabolism understood.
- Concentration reflective of uptake of cigarette smoke constituent(s).
- Sensitive and reliable analytical methods available.
- Sampling to acquire material for analysis only minimally invasive.

With these considerations in mind, smoke constituents and corresponding biomarkers of exposure were selected for analysis in this study. The biomarkers chosen, the corresponding smoke constituent, and the appropriate biofluid matrix are shown in Table 2.

[1] I.e., biomarkers of biologically effective dose and biomarkers of potential harm.

Table 2 - Biomarkers of Exposure Chosen for Evaluation

Biomarker	Sample Matrix	Smoke Constituent
Acetonitrile	Exhalate, Blood	Acetonitrile
Carboxyhemoglobin	Blood	Carbon monoxide
CO	Exhalate	Carbon monoxide
Hb adducts of 3- and 4-aminobiphenyl	Blood	3- and 4- aminobiphenyl
Nicotine and 5 metabolites	24-hr urine	Nicotine
NNAL and NNAL-glucuronide	24-hr urine	NNK

In addition to these biomarkers of exposure, the following biomarkers of effect have been selected for analysis, consistent with published investigations.

Table 3 - Biomarkers of Effect Chosen for Evaluation

Biomarker	Sample Matrix	Health Effect
HDL-cholesterol, LDL-cholesterol	Blood	Atherosclerosis
11-Dehydro-thromboxane B_2	First void urine	Platelet activation
Fibrinogen	Blood	Cardiovascular disease
8-epi-$PGF_{2\alpha}$	First void urine	Lipid peroxidation
C-reactive protein	Blood	Tissue injury
Malondialdehyde	Blood and urine	Oxidative stress

For many of the selected biomarkers of exposure, analytical methods are available but require further development or refinement.

Initial data on exposures are required to estimate sample sizes required for the larger study. The study described in this protocol has been designed to assess the feasibility of the proposed larger sample-size investigation by focusing on 1 tar yield segment and a non-smoking control population. The tar yield segment selected (3.0 to 6.9 mg tar/cigarette, as measured by FTC methods) comprises only 11% of U.S. smokers (~80% smoke higher yield cigarettes), and will challenge sample recruitment procedures. Measurement of biomarker concentrations in adult smokers of these lower yield cigarettes and the non-smoking control group will permit evaluation of the adequacy of the limits of quantification of the analytical methods.

The procedures to be employed in this exploratory study are of minimal risk to participants in the study.

3. STUDY OBJECTIVES

The objectives of this pilot study are:

- To establish the validity of the design concepts (e.g., sample collection, feasibility, and precision of analytical methods for biomarkers, sample handling and stability, data acquisition by questionnaire) to be used in a subsequent large study of adult smokers representing all tar and nicotine categories in the U.S. market.
- In particular, the study should determine
  - The intra- and inter-individual variability of each estimate of biomarkers of exposure and biomarkers of effect.
  - If the selected biomarkers of exposure and biomarkers of effect can differentiate between smokers of 3.0 to 6.9 mg tar (FTC) cigarettes and non-smokers.

4. STUDY DESIGN

This study employs a single-center, out-patient visit design. Each subject will report to the research study site at various times over the course of the 6-week study period. The visits for collection of samples/information during Weeks 1, 2, and 3 will be scheduled at the end of the 24-hour urine collections. The blood collections during Weeks 1, 2, 3, and 6 will be scheduled such that each subject has collections on 2 of his/her leisure days and on 2 of his/her non-leisure days (Note that the 24-hour urine collections during Weeks 1, 2, and 3 will be scheduled so that collections occur on 2 non-leisure days and 1 leisure day).

Blood, urine, exhalate, and spontaneous sputum samples (if any sputum samples are produced spontaneously) will be collected for determination of selected biomarkers at various times according to Table 1 during the course of the 6-week study period.

Physical examinations, 12-lead ECGs, vital signs, and laboratory evaluations (Appendix B) will be performed at Screening, Enrollment, and/or at specified times during the study (see Section 6 for specific timepoints).

5. SUBJECT SELECTION

5.1 Screening Procedures

Subjects will be recruited from the research site geographic area using advertising in print which has been approved by an Institutional Review Board (IRB) as per 21 CFR 56.

Prior to having a potential subject report to the study site, a list of telephone questions will be answered by the potential subject. The questions asked during the telephone screen will include items pertaining to age, sex, smoking status, and general inclusion/exclusion criteria. A list of sample questions that may be asked during the telephone screen are included in Appendix A.

After a successful telephone screening, the potential subject will be invited to the site for a Screening visit within 28 days of enrollment. Prior to the initiation of any study-specific procedures, the subject will be asked to provide verification of age (i.e., form of government-issued identification with birthdate and photo will be obtained from each subject and copied for site records, and the subject will be asked to sign a form confirming their age as 21 years or older). The subject's age will be verified by the site interviewer by a thorough review of the identification provided by the subject. After verification of the subject's age, he/she will be asked to read and sign a Covance CRU IRB-approved Informed Consent Form.

After the Informed Consent Form is signed, the following procedures will be performed.

1. A medical history will be obtained.
2. A 12-lead ECG will be obtained.
3. Vital signs (including oral temperature, respiratory rate, and automated seated blood pressure and pulse) will be assessed. Seated blood pressure and pulse will be measured after the subject has been seated for at least 5 minutes.
4. Blood samples for laboratory evaluations (including chemistry, hematology, complete urinalysis) and urine samples for a screen of selected illicit drugs (not including alcohol) (Appendix B) will be collected. A urine pregnancy test will be performed for female subjects of childbearing potential. (NOTE: Females who are postmenopausal [amenorrheic for a period of 1 year or more] or surgically sterile will not be required to undergo a pregnancy test.)

5. Blood samples for hepatitis and HIV screens will be collected.
6. Lung function tests (FVC and FEV1) will be conducted as exclusionary factors.
7. A screening interview will be performed by site personnel. The screening interview will consist mainly of questions related to health/medical history, concomitant medications, tobacco use history, and any intercurrent illnesses/physical findings that may be of importance during the study.

5.2 Inclusion Criteria

Subjects who meet the following criteria will be included in the study:

1. Males and females, in good health, 21 years of age and older.
2. Able to understand and willing to sign an Informed Consent Form.
3. Laboratory evaluations (including chemistry, hematology, and urinalysis) within the reference range for the testing laboratory, unless deemed not clinically significant by the Investigator.
4. Negative urine test for selected illicit drugs (does not include alcohol) at Screening and at Enrollment (Appendix B).
5. Negative urine pregnancy test for female subjects of childbearing potential at Screening, at Enrollment, and throughout the duration of the study period.
6. Smoking status defined as:

   Smokers: regular consumption of a minimum of 1 manufactured cigarette per day for a minimum of the last 12 months.

   OR Non-smokers: no smoking for the last year and/or using any nicotine-containing product such as snuff, chewing tobacco, patches, and/or sprays for 3 months prior to enrollment.
7. Smoking subjects whose cigarettes yield 3.0 to 6.9 mg tar (FTC method) per cigarette. (The tar content checked using the list of tar content.)

5.3 Exclusion Criteria

The following will exclude potential subjects from the study:

1. Persons under the age of 21 years.
2. Pregnant or nursing women.
3. Clinical manifestations of significant metabolic, hematological, pulmonary, cardiovascular, gastrointestinal, neurologic, hepatic, renal, urological, or psychiatric disorders.
4. Pulmonary function tests of <75% of the expected normal levels for FVC and FEV1.
5. Renal insufficiency as defined by serum creatinine levels of >1.3 mg/dL for females and >1.5 mg/dL for males.
6. Active fever at time of Screening or Enrollment defined as measured oral temperature greater than 100.2 °F.
7. Class III or Class IV congestive heart failure.
8. Class I or Class II congestive heart failure with decompensation in their cardiac status within the past 6 months.
9. Active and symptomatic liver disease or presence of liver enzymes more than 1.5 times the upper limit of normal.
10. Positive HIV or hepatitis result at Screening or Enrollment or at any time during the study duration.
11. Presence of an abnormal ECG at Screening, which, in the Investigator's opinion, is clinically significant.
12. History of drug addiction within 12 months prior to study entry (i.e., prior to enrollment).
13. Any other condition or prior therapy which, in the opinion of the Investigator, would make the subject unsuitable for this study.
14. Smokers:
    - Consumption of less than 1 manufactured cigarette of a specified brand per day for a minimum of 12 months.
    - Switched brands during the last 3 months prior to enrollment.
    - Smoke a brand outside of the specified range of tar delivery (3.0 to 6.9 mg/cigarette) within the last 3 months prior to enrollment.
    - Use of a different brand of cigarettes than their preferred brand at a rate of more than 10% of daily consumption during the last 3 months prior to enrollment.

- Use of any other nicotine-containing product other than manufactured cigarettes (including roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing tobacco, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) within 3 months prior to enrollment.

15. Non-Smokers:
    - History of smoking within the past 12 months.
    - History or use of any tobacco- or nicotine-containing product (including cigarette, roll-your-own cigarettes, bidis, snuff, nicotine inhaler, pipe, cigar, chewing, nicotine patch, nicotine spray, nicotine lozenge, or nicotine gum) within 3 months prior to enrollment.
16. Donation or receipt of whole blood or blood products within 3 months prior to enrollment, or during the study period.
17. Participation in a clinical study for an investigational drug, device, or biologic within 3 months prior to enrollment.
18. Any person who is a current or former employee of the tobacco industry, or their first-degree relatives (parent, sibling, child).
19. Any person who is a current employee of the contract research organization (i.e., Covance), or their first-degree relatives.

6. STUDY PROCEDURES

6.1 Enrollment Procedures

On the day of enrollment into the study, subjects will report to Covance CRU at a pre-arranged time. The following procedures will be performed at the time of enrollment.

1. A physical examination (including weight measurement) will be performed.
2. An interim medical history will be performed during which the subjects will be queried as to the occurrence of any acute illnesses since screening and any current medications and respective doses.
3. Vital signs (including oral temperature, respiratory rate, and automated seated pulse and blood pressure) will be assessed. Seated pulse and blood pressure will be measured after the subject has been seated for at least 5 minutes.

4. Phenotyping for CYP1A2 and NAT2 activity using caffeine for the test.
5. Blood samples for laboratory evaluations (including chemistry, hematology, complete urinalysis), HIV and hepatitis screens, and urine samples for a screen of selected illicit drugs (not including alcohol) (Appendix B) will be collected.
6. Urine pregnancy test for female subjects of childbearing potential.
7. Administration of questionnaire by a trained interviewer (Appendix E).
8. Collection of spontaneous sputum samples (if any produced by subject).

Any occurrence of illness reported by the subject at this interim medical history would be recorded as an intercurrent illness in the subject's case report form. Any changes in medications from Screening to Enrollment will be documented.

The phenotyping of the subjects for the CYP1A2 and NAT2 activities will be performed at this visit. The subject will be asked to refrain from consumption of caffeine or methylxanthine-containing products for a minimum of 8 hours before reporting to the site (the subjects will be instructed in the foods/drinks to avoid at their Screening visit and again before their Enrollment visit). After collection of any blood/urine samples for other analytes/screens, the subject will be given 200 mg caffeine (No-Doz®, 1 caplet at 200 mg) with 240 mL of water. A urine sample for the phenotyping will be collected between 4 and 5 hours after the caffeine administration (see Appendix C for collection procedures). A light caffeine-free meal may be provided for the subjects after the administration of the caffeine dose.

In order for the subjects to continue their participation in the study the urine drug screen must be negative and the urine pregnancy tests for female subjects must be negative.

The subjects will be administered a questionnaire at the time of enrollment into the study that will allow the collection of further data relating to such items as demographics, exposures (i.e., occupational, hobbies, household, solvents), exposure to other people's tobacco smoke, home heating/ventilation systems, dietary characteristics, use of non-tobacco nicotine products, and physical activity for all subjects. Smoking behaviors/consumption for smokers will also be investigated.

The subjects will be instructed in the collection of spontaneous sputum samples. They will be asked to produce a sputum sample, if possible. The necessary collection vessels for the collection and storage of any sputum samples will be given to the subject. They will be instructed to try to obtain a sample on the morning of their next site visit.

6.2 Visit Schedule

Subjects will be requested to alter their daily routines very minimally in order to be available for site visits and sample collections. The visits will be scheduled such that the visit will occur at the end of the 72-hour collection period of the diary/cigarette butts during Weeks 1, 2, 3, and 6. Because of the extended collection of the diary and urine samples, the visits will be scheduled no less than 4 days apart.

So as to interrupt regular smoking behaviors as minimally as possible, smoking subjects will be allowed to smoke during the site visits.

After enrollment, subjects will be requested to visit the research site during 4 occasions. These visits will be scheduled such that the subject will visit the site and undergo the blood collections on 2 of his/her leisure days and on 2 of his/her non-leisure days. The visits during Weeks 1, 2, and 3 will be scheduled at the end of the 24-hour urine collection and will be split so that the subjects are completing the collections of urine on 2 of their non-leisure days and 1 of their leisure days. The Week 6 visit will be scheduled at the subject's convenience on a leisure day (due to split of Week 1, 2, and 3 visits, the Week 6 visit must be a leisure day visit).

If a subject is unable to report to the site during one of the first 3 weeks, a visit may be re-scheduled during Weeks 4 or 5 to make up for the missed visit. The collection of samples will be in sequential order even if a week is missed. The actual calendar dates of collection will be recorded on the samples. The subject may schedule the Week 6 visit ± 1 week from the "nominal" scheduled timepoint for the final visit (i.e., there will be a 14-day window for the final site visit).

Study procedures to be performed at the respective visits are outlined in Table 1 of this protocol. At the enrollment visit, the subject will be given the supplies he/she needs to collect the separate void (immediately after waking), 24-hour urine sample, 72-hour diary, cigarette butts, cigarette packs, and spontaneous sputum sample for the Week 1 visit. The subjects will be given instructions on the collections and the Week 1 visit will be scheduled. The same procedures will be performed at the subsequent visits (i.e., when the subject returns the samples for Week 1, they will be given the supplies for collection of urine [both first void and 24-hour collection], diary, cigarette butts, cigarette packs, and sputum for Week 2, etc.)

At each site visit, the subjects will undergo the following procedures: vital signs measurement, HDYF? inquiry, assessment of concomitant medications, collection of any spontaneous sputum samples (both those collected at home or those able to be produced at the site), blood sampling (both for selected biomarkers [certain markers are not tested at every visit] and for HIV/hepatitis screens [tested at every visit]), exhalate sampling/testing for respective biomarkers, and a urine pregnancy test for females of childbearing potential. At site visits on Weeks 1, 2, and 3, the subjects will return the urine collection containers from the first voids and the 24-hour collections.

At every site visit after enrollment the subjects will be asked a series of questions (i.e, the weekly survey). Any reported changes in smoking status/behaviors will be documented. The subjects who smoke will also be asked when the most recent cigarette was consumed (i.e., they will be asked when they had the cigarette closest to the research site visit time).

6.3 Smoking Exposure/Consumption Diary

A diary will be given to each subject before the scheduled urine collections during Weeks 1, 2, 3, and 6. Each subject will be instructed to record activities relating to exposure to other people's tobacco smoke (non-smoking subjects) and/or smoking consumption (if a smoking subject) during the 72 hours before reporting to the research site. Separate diary types (i.e., with separate instructions) will be provided to smokers and non-smokers.

6.4 Concomitant Medication

Any medication taken by a subject during the course of the study and the reason for its use will be documented during each site visit and in the case report form (CRF).

6.5 Selection of Subjects

Male and female subjects, a total of approximately 135 (approximately 70 smokers and 65 non-smokers), will be selected and enrolled into the study from those subjects who meet all the inclusion criteria and have none of the exclusion criteria. The subjects will be distributed approximately equally between adult males and adult females for the smokers and non-smokers.

At the time of the Screening visit, after the Informed Consent Form has been signed by the potential subject and a witness, the potential subjects will be given a screening number by which to have their screening samples tracked. The screening number will consist of the letter "S" followed by a 3-digit unique subject identification number (e.g., S001 would be the first screening subject). If the subject is approved for the study, the subject will be assigned a number by Covance CRU staff which consists of the Sponsor's Project Number followed by a 3-digit unique subject identification number (e.g., Subject Nos. 1148-001 to 1148-135). Assignment of numbers will be performed based upon the subject's gender and smoking status as follows:

Subject Numbers 1148-001 through 1148-035 will be adult female smokers.
Subject Numbers 1148-036 through 1148-070 will be adult male smokers.
Subject Numbers 1148-071 through 1148-103 will be adult female non-smokers.
Subject Numbers 1148-104 through 1148-135 will be adult male non-smokers.

Assignment of subject numbers will occur in ascending order within the subgroups (as delineated above) and no numbers will be omitted. (NOTE: the screening number and the subject number assigned for the remainder of the study will not be the same.) Subject numbers will be used on all study documentation.

Adult smoking subjects who decide to stop smoking during the study period, but are otherwise still able to continue in the study, will be allowed to remain in the study population and will receive all benefits to which they are entitled. Adult smoking subjects who use a tobacco product other than manufactured cigarettes (e.g., cigar or pipe) will be dismissed from the study population and will be given benefits as determined on a case-by-case basis.

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Principal Investigator may remove a subject from the study if, in the Principal Investigator's opinion, it is not in the best interest of the subject to continue the study. Notification of discontinuation will immediately be made to the Sponsor and to the Study Monitor. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's CRF.

6.6 Sample/Information Collections

Blood/plasma and urine sample splits will be provided to the Sponsor's laboratory (INBIFO) for comparison of results from tests of hemoglobin adducts of 3- and 4-aminobiphenyl, nicotine and nicotine metabolites, NNAL, and NNAL-glucuronide. A total of approximately 12% of the subjects (16 random subjects total – 4 from each subgroup included in the study) in the study will have their collected samples split and sent to the Sponsor's laboratory for analysis.

Plasma and urine sample splits will be provided to an independent laboratory (University of Texas Southwestern Medical Center) for comparison of results of malondialdehyde. A total of approximately 12% of the subjects (16 subjects total – 4 from each subgroup included in the study) in the study will have their collected samples split and sent to the Sponsor's laboratory for analysis.

These sample splits will be required to have negative results of HIV and Hepatitis B and C virus screens to meet specifications of the receiving laboratory. (Sample submission is described in a subprotocol.) All subjects enrolled in the study will sign a consent form to have this testing completed; and, therefore, any subset corresponding to 12% of the total number of subjects will have documented results of the HIV and hepatitis screens. If a subject is discontinued from the study for any reason prior to the Week 6 visit, a different subject's samples will be chosen for the method comparisons using the randomization schedule as generated by a Covance CRU Biostatistician.

6.6.1 Lung Function Tests

At Screening, all of the subjects will undergo a lung function test to determine eligibility for the study. Spirometry measurements will be conducted at the research site using a Spirometrics FLOWMATE V PLUS spirometer (Spirometrics Medical Equipment Company). The subjects will be instructed in the performance of the tests prior to the measurements being recorded. If necessary, 2 measurements may be conducted to ensure the subject's understanding of the instructions/instrument. If the subject's results are satisfactory and meet the entrance criteria on the initial measurement, the second try will not be necessary. If, however, the subject's results do not meet the entrance criteria on the initial measurement, the subject will be given a second attempt. In order to be eligible for the study, the FVC and FEV1 measurements must be >75% of the expected values.

6.6.2 Blood Sample Collection for Biomarker Analysis

Blood samples will be collected by research site phlebotomists in separate collection tubes as outlined below. The blood collections will be scheduled such that the analytes with 4 collection timepoints will be performed such that 2 collections will be performed on the subject's respective leisure-days and 2 collections will be performed on the subject's respective non-leisure days. The analytes with 3 scheduled collections will be attempted to be collected on 2 non-leisure days and 1 leisure day.

Table 4 - Biomarkers to be Tested in Blood and/or Plasma Samples

Biomarker	Sample Matrix/Number of Aliquots /Volume Needed	Collection Schedule
Acetonitrile	Whole Blood, 1 aliquot, 6 mL	Weeks 1, 2, 3, and 6
Carboxyhemoglobin	Whole Blood, 1 aliquot, 3 mL	Weeks 1, 2, 3, and 6
Hemoglobin adducts of 3- and 4-aminobiphenyl	RBCs from 10 mL whole blood, 1 RBC pellet for each analytical laboratory = 2 total	Weeks 1 and 6
Malondialdehyde	Plasma, total of 4 aliquots (2 for each analytical laboratory), 1.5 mL each aliquot (plasma obtained from centrifugation of tubes used for hemoglobin adducts during Weeks 1 and 6 and from separately drawn 10 mL tube on Week 3)	Weeks 1, 3, and 6
HDL-cholesterol, LDL-cholesterol, C-reactive Protein	Serum, 1 aliquot of 2 mL	Weeks 1, 3, and 6
Fibrinogen	Plasma, 1 aliquot, minimum 1 mL	Weeks 1, 3, and 6

6.6.3 Blood Sample Collection for Safety Evaluation

Blood samples for chemistry determinations will be collected using SST tubes (to obtain approximately 2 mL of serum) and blood samples for hematology determinations will be collected using a 3 mL K_3EDTA tube. Blood samples for chemistry and hematology will be collected at Screening and Enrollment.

Collection of blood samples for the HIV Antibody, Hepatitis B Surface Antigen, and Hepatitis C Antibody screens will be performed at every site visit.

All blood samples for chemistry, hematology, and HIV/hepatitis screens will be analyzed by Covance Central Laboratories. Processing, storage, and shipping procedures will be as described in Covance CRU Standard Operating Procedures and Appendix C.

6.6.4 Urine Sample Collection

A total of 3 urine collections will be performed by the subjects outside of the research site, over 24-hour intervals, for determinations of the biomarkers listed in Table 5. The collections will be scheduled such that 2 of the collections will occur during the subject's respective non-leisure days and 1 of the collections will occur during the subject's respective leisure days.

The subjects will be given a smaller urine collection cup, a urine collection device, a large collection container, and a cooler-type storage unit (equipped with ice packs/cooling packs) prior to their scheduled collection period. The subjects will be instructed to collect a separate sample that is obtained just after waking on the days prior to site visits during Weeks 1, 2, and 3 for analysis of the 11-dehydro-thromboxane B_2 and 8-epi-$PGF_{2\alpha}$. After that individual collection, each void will be collected in the urine collection device and transferred to the large collection container. Subjects will be instructed on the need to keep the contents of the smaller collection cup frozen and the large collection container cool during the entire collection interval and until the samples are returned to the research site.

Table 5 - Biomarkers to be Tested in Urine Samples

Biomarker	Number of Aliquots/ Aliquot Size	Collection Times
Malondialdehyde	4 aliquots of 4 mL each	Weeks 1, 2, and 3
*Nicotine and nicotine metabolites	4 aliquots of 4 mL each	Weeks 1, 2, and 3
*NNAL and NNAL-glucuronide	7 aliquots of approximately 100 mL each	Weeks 1 and 3
**11-Dehydro-thromboxane B_2	2 aliquots of 5 mL each from a first upon waking void	Weeks 1, 2, and 3
**8-epi-$PGF_{2\alpha}$	2 aliquots of 5 mL each from a first upon waking void	Weeks 1, 2, and 3
Urine creatinine (24-hour)	1 aliquot of 10 mL	Weeks 1, 2, and 3

*The results of these analyses will be reported as mass/volume, mass/24 hours, mass/mg creatinine, mol/24 hours, and mol/mg creatinine, with the creatinine determined as a 24-hour result on the samples received for these analyses.

**The results of these analyses will be reported as mass/volume, mass/mg creatinine and mol/mg creatinine, with the creatinine determined as a spot determination on the samples received for these analyses.

Processing, storage, and shipping instructions for urine samples are presented in Appendix C.

6.6.5 Safety Evaluation Urine Sample Collection

Urine samples will be collected for urinalysis at Screening and Enrollment (Appendix B).

A urine sample will be collected at Screening and Enrollment for a urine drug screen that includes assays for selected narcotics and selected illicit drugs.

A urine sample will also be collected from female subjects of childbearing potential (i.e., those not postmenopausal [amenorrheic for a period of 1 year or more] or surgically sterile) for pregnancy testing at each site visit. This test will be performed at the study site using a commercially available kit. If a female subject should become pregnant while enrolled in the study, that subject will be immediately discontinued from participation in the study, informed of the possible risks to the fetus by the maternal behaviors (i.e., smoking/drinking), and referred to her primary care provider.

All urine samples for safety evaluations (with exception of the urine pregnancy test) will be analyzed by Covance Central Laboratories. Processing, storage, and shipping procedures will be as described in Covance CRU Standard Operating Procedures.

6.6.6 Exhalate Sample Collection for Determination of Acetonitrile and Determination of Carbon Monoxide

Exhalate samples (up to a total possible volume of 500 mL at each timepoint) will be collected in Tedlar® bags for the determination of acetonitrile during visits at Weeks 1, 3, and 6. Prior to collection of the exhalate sample, the smoking subjects will be asked the approximate time of their last cigarette and that information will be recorded. Processing, storage, and shipping procedures will be as described in Appendix C.

Additionally, at the site visits during Weeks 1, 2, 3, and 6 the subject's exhalate level of carbon monoxide (CO) will be determined by technicians at the research site using a Micro Medical MicroCO Meter (Micro Direct, Inc., Lewiston, ME). This monitor, which is commercially available, is based on an electrochemical fuel cell sensor, which works through the reaction of CO with an electrolyte at one electrode and oxygen at the other. Details on operation of the instrument are included in Appendix C. Results obtained by the instrument will be recorded in each subject's respective CRF.

6.6.7 Sputum Samples

Subjects will be given a sterile container for collection of spontaneous sputum samples on the morning of their scheduled site visit. The subject will be asked and instructed to collect any sputum sample in the morning of the day they are scheduled to return to the research site (i.e., when they are scheduled to return the urine collection containers and the diaries). When the subject returns to the site, if they were not able to produce a sputum sample at home, they will be asked to collect any spontaneous sputum samples that occur while they are at the research site. The sample will be stored frozen until the end of the study period, at which time they may be processed and analyzed further (as described in Appendix C).

6.6.8 Un-Smoked Cigarette Portion/Pack Collections

The smoking subjects will be given a HDPE container into which they will be asked to collect their unsmoked cigarette portions (including filter) during a 72-hour period prior to the research site visits during Weeks 1, 2, 3, and 6 (i.e., during the diary recording interval).

The subjects will also be given a ziplock bag into which to collect their empty cigarette packs during a 72-hour period prior to the research site visits during Weeks 1, 2, 3, and 6. The packs will be used for verification of the brand/type of cigarette filters returned to the site, and any discrepancies will be noted. If the subject reports to the site with a pack that is not empty, a photocopy of the pack will be obtained. After verification of the brand/type of cigarettes, all packs will be photocopied and the empty packs will be destroyed/discarded by the research site (any packs that still contain cigarettes will be returned to the subject).

The filters collected will be counted, processed as per Appendix C, and sent to the Sponsor's laboratory (INBIFO) for analysis according to subprotocols. The number of collected cigarette portions and packs will be compared to the recorded smoking consumption in the subjects' diary. Any discrepancies between the recorded amount and the number of butts/packs submitted will be recorded.

6.6.9 Questionnaire

During visits at Enrollment and Week 6, the subjects will be administered a questionnaire (Appendix B). This tool will allow the collection of in-depth demographics, exposure to ETS, exposure to other agents that may affect biomarkers, and lifestyle/health/dietary information.

After collection of blood and/or urine samples, the subject will be escorted by a trained interviewer to an area separate from other procedures being performed. The interviewer will be seated at a computer terminal and the subject will be placed such that he/she cannot see the screen but that he/she has face-to-face interaction with the interviewer. Both people will have a hard copy of the questionnaire for ease of following the questions and giving/recording answers. Answers given from the subjects will be recorded directly into the computer system by the interviewer.

The interviewer will read aloud the questions as they appear on the computer monitor/hard copy. The subject will be instructed to answer to the best of his/her ability. All efforts will be made to have the subject answer all questions; however, if a subject refuses to answer any specific question, the refusal will be noted by the interviewer. If the subject asks for clarification or indicates confusion about the intent of the question, the interviewer will mark a check box on the computer screen to indicate the subject's confusion. This will allow for an exploration of questions that may need to be examined further before the larger Total Exposure Study (TES).

At the Week 6 interview, any discrepancies from the initial questionnaire will be noted. At the end of the interview, if any discrepancies exist, they will be brought to the interviewer's attention. At that point, the subject will be queried further for reasons regarding the discrepancies.

6.6.10 Vital Signs

Vital signs (including oral temperature, respiratory rate, and automated seated blood pressure and pulse) will be obtained at Screening, at Enrollment, and at each site visit.

Seated blood pressure and pulse will be measured after the subject has been seated for at least 5 minutes.

6.6.11 12-Lead ECGs

A 12-lead ECG will be obtained at Screening only as an exclusionary measure.

6.6.12 HDYF? Inquiry/Weekly Survey

Subjects will be asked a non-leading How Do You Feel? (HDYF?) question such as "Have there been any changes in your health status since you were last asked?" at the time of each post-enrollment vital signs measurement. Any changes in status will be recorded as an intercurrent illness in the subject's CRF.

At each site visit during Weeks 1, 2, and 3, the subjects will be asked a series of questions relating to exposures to tobacco smoke (household, transportation, and occupational), primary activities within the last 8 to 10 hours, transportation, and smoking consumption for smoking subjects (Appendix E). Additionally, before collection of any blood/urine/exhalate samples, the smoking subjects will be asked for the approximate time of their last cigarette.

6.6.13 Physical Examinations

A physical examination will be performed at Enrollment.

6.7 Analytical Methodology

Analytical methodology for the determinations of the biomarkers in this study will be based upon published methods where available. If no published method is available, a method will be developed and validated by the analytical laboratory prior their use in this study. Validation of each method will be approved by the Sponsor.

The analytes, the laboratory performing the analysis, the proposed method, and the published method are presented in Table 6.

Table 6 Analytes, Methods, and Published References

Biomarker/Matrix	Analysis Site	Proposed Method	Reference Number/Additional Information
Acetonitrile in Blood	Covance Laboratories - Madison	Headspace GC	Ref. 3
Acetonitrile in Exhalate	Covance Laboratories - Madison	Thermal Desorption GC-NPD	Ref. 4, 5
Carboxyhemoglobin in Blood	Covance Central Laboratories	IL Multi-4 CO-Oximeter (Serial No. 01000875)	See manufacturer's operating manual
Hemoglobin Adducts of 3- and 4-Aminobiphenyl in RBCs	Covance Laboratories – Harrogate*	GC with negative-ion chemical ionization MS detection	Ref. 6
HDL-cholesterol and LDL-cholesterol in Serum	Covance Central Laboratories	Standard CAP and CLIA methods	Not applicable
Malondialdehyde in Blood and Urine	Covance Laboratories – Harrogate **	1,3-cyclohexanedione derivatization and HPLC with fluorescence detection.	Ref. 7
C-Reactive Protein in Serum	Covance Central Laboratories	Dade Behring Nephelometer	See manufacturer's operating manual
Fibrinogen In Plasma	Covance Central Laboratories	MLA 1600	See manufacturer's operating manual
Nicotine and Metabolites in Urine	Covance Laboratories – Harrogate*	LCMSMS	Ref. 8
NNK Metabolites in Urine	Covance Laboratories – Madison*	GC with TEA detection	Ref. 9
11-Dehydro-thromboxane B_2 in Urine	Covance Laboratories - Harrogate	Microplate immunoassay	Cayman Chemical catalog no. 519501
8-Epi-$PGF_{2\alpha}$ in Urine	Covance Laboratories - Harrogate	Microplate immunoassay	Cayman Chemical Catalog no. 516351
Carbon Monoxide in Exhalate	Covance Clinical Research Unit	Micro Medical MicroCO Meter	See manufacturer's operating manual

* A sample split will be provided to the Sponsor's laboratory (INBIFO) for comparison of results. A total of approximately 12% of the subjects (16 subjects total – 4 from each subgroup included in the study) in the study will have their collected samples split and sent to the Sponsor's laboratory for analysis. The details are provided in a subprotocol.

** A sample split will be provided to an independent laboratory (University of Texas – Southwestern Medical Center) for comparison of results. A total of approximately 12% of the subjects (16 subjects total – 4 from each subgroup included in the study) in the study will have their collected samples split and sent to the independent laboratory for analysis. The details are provided in a subprotocol.

6.8 End of Study Procedures

The following procedures will be performed at study completion (i.e., Week 6):

1. Vital signs (including oral temperature, respiratory rate, and automated seated blood pressure and pulse).
2. HDYF? inquiry/weekly survey.
3. Blood sample collection (both for biomarker analysis and HIV/hepatitis screen), exhalate collection/testing, and spontaneous sputum samples collection (if any produced by subjects).
4. Urine pregnancy test for female subjects of childbearing potential.
5. Assessment of concomitant medications.
6. Administration of questionnaire (repeat questionnaire from enrollment). If any discrepancies from enrollment questionnaire are noted, the subject will be queried and an attempt will be made to resolve the discrepancy or obtain a reason for the change.

7. REMOVAL OF SUBJECT FROM STUDY PARTICIPATION

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Principal Investigator may remove a subject from the study if, in the Investigator's opinion, it is not in the best interest of the subject to continue the study, such as, the occurrence of an exclusion criterion which is clinically relevant and affects subject safety. Notification of discontinuation will immediately be made to the Sponsor and Study Monitor. In the case of premature discontinuation of study participation, efforts will be made to perform all final study day assessments and the Study Completion Page of the CRF will be completed. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded on the subject's CRF.

8. STATISTICAL ANALYSES

8.1 General Purpose for Analysis

The pilot study for the TES is an observational study which will, among other objectives, examine the validity of the acquisition of data by questionnaire and diary for use in interpreting data obtained on various biomarkers. The study will determine the intra- and inter-individual variability of each estimate of smoke constituent uptake in adult smokers of cigarettes in the 3.0 to 6.9 mg tar range and of non-smokers.

The data analysis plan will involve several strategies to examine the data that are collected. These strategies include:

- Descriptive analyses aimed at describing the study participants;
- Presentation of estimates of biomarkers; and
- Modeling of the biomarkers to characterize the relationships between the biomarkers and study variables.

The descriptive analyses will provide a demographic profile of the subjects according to smoking status (smokers and non-smokers). Descriptive statistics for questionnaire items will compare the responses provided by smokers and non-smokers.

Estimates of biomarkers will be provided for both groups (smokers and non-smokers) and by demographic characteristics (e.g., gender, education). In addition to obtaining estimates of the biomarkers, relationships between the biomarkers and estimates of external exposure will be examined by comparing the machine derived estimates (FTC value) and the number of cigarettes smoked. Further detail on each of these analyses is provided in the sections below.

8.2 Descriptive Presentation of Data

Univariate measures such as the frequency, mean (arithemetic and geometric), standard deviation, standard error, median, quantiles (5^{th} and 95^{th} percentiles), and range will be used to describe the study variables and to descriptively examine any relationships that study variables may have with the outcomes of interest, biomarker measures. Screening variables that are used only to determine study eligibility will not be included in the descriptive presentation. The variables will be summarized both statistically and graphically. The descriptive statistics and graphics will aid in identifying statistical outliers, determining the mathematical form of the underlying distribution, and in summarizing the data. All of the descriptive statistics will be performed for each collection time separately and for the mean of all the collection times.

The data will be examined to identify statistical outliers using graphical displays such as the box plot and stem-and-leaf graphs. If possible, information from the questionnaire will be used to aid in identifying the reason such observations have been identified as outliers. The outliers will be evaluated carefully and will be excluded only if they can be attributed to error and cannot be corrected. If an examination of the data fails to produce an explanation for the outlier, other robust evaluation procedures may be employed to aid in providing estimates that are less sensitive to the occurrence of outliers.

The data will also be examined to identify missing data. Whenever missing data occur, an attempt will be made to determine why the data are missing. Missing data may occur due to incomplete data collection or non-response to a questionnaire item. Where possible, an effort will be made to obtain the missing data. Other options for missing data include imputing the data, carrying forward the last observation, and elimination.

8.3 Descriptive Statistics for Selected Questionnaire Variables

Overall summary descriptive statistics for the demographic variables of interest for smokers and non-smokers will be used to provide a descriptive profile of the study subjects. The number (n) and percentage (%) for each demographic categorical variable for smokers and non-smokers will be presented. For the analytical data and continuous variables obtained from the questionnaire or physical examination, the following statistics will be presented for each tar group and overall: number (n), mean, standard deviation, median, minimum, and maximum.

Comparisons between smokers and non-smokers can be made for variables of interest using the t-test, U-test, or the chi-square test as appropriate.

8.4 Descriptive Statistics of Biomarkers of Exposure and Effect

Biomarkers of exposure (previously described) will be measured in either urine, blood, and/or exhaled air and will be used to estimate smoke uptake. In particular, for nicotine and NNK, the sum of their respective metabolites will be used to provide estimates of smoke uptake. Biomarkers of effect will be measured in sputum (if any produced), blood, and/or urine.

Separate analyses will be performed for each biomarker for smokers and non-smokers. Summary demographic statistics for each biomarker to include the mean, median, standard deviation, minimum, and maximum will be determined for the smokers and non-smokers and by demographic variables of interest. Graphical displays, such as box plots, will be used to examine the distribution of the data values and to identify outliers.

8.5 Statistical Tests

The estimates of the biomarkers of exposure and variables such as demographics, lifestyle, and environmental factors will be compared between the 2 groups (smokers of 3.0 to 6.9 mg tar brands and non-smokers) using an appropriate parametric or non-parametric approach for each collection time separately and for the mean of all collection time points.

8.6 Exposure Response Modeling

8.6.1 Basic Modeling

Exposure-response relationships will be evaluated to characterize the relationship between the biomarkers and estimated daily exposure at each collection time separately and for the mean of all collection times. With recognition that the actual dose of a cigarette is unknown, the estimated external exposure will be approximated using machine derived data and/or the number of cigarettes smoked during the analysis period. Results from the Massachusetts Benchmark Study (1999; Ref. 10) indicate that "... vapor phase smoke constituents are best described by carbon monoxide, while either nicotine or 'tar' describes particulate phase components equally well." The FTC tar or the FTC CO values will be used for all other biomarkers with the assumption that all other smoke constituents are either proportional to tar (particulate phase constituents) or to CO (gas phase constituents). The average number of cigarettes smoked daily will be determined by a weighted average of the number of cigarettes consumed each day that is not a leisure day and the number of cigarettes smoked each day that is a leisure day.

In the first basic approach, no additional explanatory variables or covariates will be introduced in the models to describe the exposure-response relationships. The results of the biomarker determinations for the non-smoking group will be included in the regression analysis to estimate the intercept (baseline) of the models. Quasi-likelihood estimation will be used to determine the parameter estimates. If variance heterogeneity occurs, suitable variance functions will be introduced into the regression models. The following non-linear regression model (Ref. 11; Gompertz, asymmetric sigmoid shape) will be considered with exposure as variable x and biomarker mean response as μ:

$$\mu = a(\exp(-\exp(-b(x-c))))$$

If the biomarkers of exposure are found to correlate with estimated external exposure, the relationship between the biomarkers of exposure and biomarkers of effect will be determined.

8.6.2 Model Refinement

An attempt will be made to refine the regression model by adding variables from the questionnaires, diaries, and safety data to the model. This includes variables that are related to smoking behavior, metabolism, health status, bodyweight index, etc. This can be done only by an explorative approach. Graphs (biomarker estimates will be plotted against study variables identified from the questionnaire) will be used to help identify potential important influence parameters, which may be included in a multivariate regression model such as the multilinear regression model, including forward, backward, and stepwise parameter elimination.

Throughout the model-building process, attention will be given to identifying observations that do not fit the hypothesized model(s) well, or that have an unusually strong impact on the model parameters or predictive power. Influence diagnostics will be examined to identify influential observations. To assist in understanding any influential observations, data from the questionnaire will be reviewed, and observations may be excluded from the analyses. Regression models will also be assessed for adequacy and goodness of fit.

As model building proceeds, preliminary results will be shared with the Sponsor, who may request additional analyses in order to accomplish the study objectives.

8.7 Intra-Subject and Inter-Subject Variability

The pilot study will examine whether multiple sample collections should be obtained for each subject. Depending on the biomarker there will be 2, 3, or 4 sample collection times. A mixed-effects analysis of variance model will be used to model the effect over time for each biomarker. Such a model accounts for the within-subject correlated observations. Three correlation structures will be considered: compound symmetric (assumes a common correlation over time), auto-regressive (based on a single correlation value that diminishes with time), and the unspecified structure. The choice of correlation structure will be made based on Akaike's criterion. The model for the mean will be parameterized to include an effect over time, group classification (smoker of 3.0 to 6.9 mg tar [FTC] yield per cigarette versus non-tobacco user), important covariates of interest (e.g., demographics, leisure day versus non-leisure day sample identifier, etc.) that may be time-dependent covariates, and time by covariate interactions. The usual F test with Satterthwaite's adjusted degrees of freedom will be used to test for important effects. This model will facilitate the estimation of intra-subject variability and inter-subject variability while estimating the effect of important factors of interest.

Multiple correlation coefficients will be estimated relating each biomarker with the set of predictor variables. A test for significance of each estimate will be based on an F test (Ref. 12).

8.8 Supplementary Analyses

Other additional exploratory analyses of interest will be performed, as warranted, to accomplish the study objectives. As an example, there exists in the literature reports which claim to have found correlation between subjective ETS exposure estimates and measured biomarker levels. Since biomarker levels are to be measured in the non-smoking group in the Pilot Study, it is of interest to take advantage of the availability of the biomarker data and explore whether any relationship can be established between measured biomarker levels and subjective ETS exposure estimate.

The objective of the analysis is to compare estimated ETS exposure from the questionnaire response with the measured levels of biomarkers of exposure for the non-smoking subject group. Nicotine metabolites (both individually and combined) and 4-ABP Hb adducts were chosen as the ETS exposure biomarkers for this study. The choice is based on consideration of (i) the specificity of the biomarkers for exposure to cigarette smoke constituents, (ii) published studies reporting correlation of these biomarkers with estimated ETS exposure (Ref. 13, 14, and 15) and (iii) sensitivity of analytical methods (originally designed to detect levels in smokers) required to quantify the levels of these biomarkers among nonsmokers.

Levels of the biomarkers for the ETS exposed and the non-exposed non-smokers will be compared. Biomarker levels for the exposed group will be further compared with various ETS exposure indices based on the questionnaire data, e.g., duration/weighted duration, cumulative exposure/average exposure, etc., for individual settings such as home, workplace, etc., and integrated exposure from more than one setting.

The 10% random subset of blood and/or urine samples of the total number of subjects for determinations of hemoglobin adducts, nicotine and nicotine metabolites, NNK metabolites, and malondialdehyde analyzed by 2 separate laboratories will be statistically compared using an appropriate parametric or non-parametric approach.

8.9 Sample Size

The sample size for this study was selected empirically to determine the procedures and best design aspects for the total exposure study, and was not based on power calculations.

9. ADMINISTRATIVE ASPECTS

9.1 Change in Protocol

There will be no alterations in the protocol without agreement between the Sponsor and the Principal Investigator.

There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, Covance CRU, and the Covance CRU IRB.

9.2 Investigator Meeting

Prior to the start of the study, the representative(s) of the Sponsor will meet with the Investigator(s) and appropriate Covance CRU staff to familiarize the Investigator and staff with the materials necessary for conducting the study.

9.3 Disclosure

All information provided regarding the study, as well as all information collected during the course of the study, will be regarded as confidential. The Principal Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

9.4 Monitoring

This study will be conducted in accordance with Good Clinical Practices (GCPs). A monitor from J. Tyson & Associates, Inc., will monitor the trial. The Monitor will arrange regular visits to the trial center, as appropriate, to check the progress of the study and to review and collect completed CRFs.

During monitoring visits, the monitor will:

- Help resolve any problems.
- Examine all CRFs for omission of data, compliance, and possible intercurrent illnesses.
- Discuss inconsistencies in the study data.
- Ensure that all study materials are correctly stored and dispensed.

- Check adherence to the obligations of the Investigator(s).
- Review consent forms, in particular the date of consent, signature, and verification of subject's age.
- Perform Source Data Verification, as described below.

In line with ICH GCP guidelines, monitoring will include verification of data entered in the CRF against original subject records. This verification will be performed by direct access to the original subject records and the Sponsor, Monitor, and any designees guarantee that subject confidentiality will be respected at all times. Participation in this study will be taken as agreement to permit direct source data verification.

In addition, representatives of the Quality Assurance Department of the Sponsor (or equivalent), or appointed monitoring organization(s), may request to inspect the study documents (study protocol, CRFs, original files, etc.). All subject data shall be treated confidentially.

During the course of the study, the CRFs shall be forwarded to the Data Services and Biostatistics Department of Covance Clinical Research Unit. All reports of monitoring activities will be forwarded to both Covance Clinical Research Unit Data Services and Biostatistics Department and the Sponsor.

The Study Protocol, each step of the data-recording procedure, and the handling of the data, as well as the study report, may be subject to independent review by the Quality Assurance Department of the Sponsor (or equivalent). Audits may be conducted to assure the validity of the study data.

9.5 Institutional Review Board

In accordance with 21 CFR 56, the protocol, advertisements, and Informed Consent Form will be reviewed and approved by the Covance CRU IRB. The Sponsor will supply relevant material for the Principal Investigator to submit to the Covance CRU IRB for the protocol and Informed Consent Form review and approval. Verification of the Covance CRU IRB approval of the protocol and the written Informed Consent Form will be transmitted to the Principal Investigator.

The Covance CRU IRB will be informed by the Principal Investigator of subsequent protocol amendments. IRB approval for protocol amendments will be transmitted in writing to the Principal Investigator.

The Principal Investigator will provide the Covance CRU IRB with progress reports at appropriate intervals (not to exceed 1 year) and a Study Summary Report following the completion, termination, or discontinuation of the Principal Investigator's participation in the study.

9.6 Informed Consent

Written informed consent for the study will be obtained from all subjects before protocol-specific procedures are carried out. The Informed Consent Form generated by the Principal Investigator (or designee) will be approved along with the protocol by the Covance CRU IRB and will be acceptable to the Sponsor. Elements to be included in the informed consent form are outlined in Appendix D.

The Principal Investigator (or designee) will explain the nature of the study. The subject will be informed that participation is voluntary and that they may withdraw from the study at any time. In accordance with 21 CFR 50, informed consent shall be documented by the use of a written consent form approved by the Covance CRU IRB and will be signed by the subject prior to protocol-specific procedures being performed.

The subject will be given a copy of the consent and the original will be maintained with the subject's records.

9.7 Records

The results from Screening and data collected during the study will be recorded in the subject's CRF, which will be designed and printed by Covance CRU. All entries will be made in black ink. Entry corrections will be made by drawing a single line through the error, entering the correct data, and initialing and dating the entry by the individual responsible for transcribing the data. The Principal Investigator (or designee) will review and sign all CRFs. In order to maintain confidentiality, the subject will be identified only by his/her subject number. Information gathered through the use of the questionnaire will be captured directly into a computer system and transferred to Covance Clinical Research Unit for inclusion in analysis.

The completed original CRF will be transferred to the Monitor. Copies of each CRF will be retained by the Principal Investigator. All source documents, records, and reports will be retained by Covance CRU in accordance with 21 CFR 312.62(c).

All primary data, or copies thereof (e.g. laboratory records, CRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report will be retained in the Covance archives. The study report will be retained in the Covance archives for a period of 20 years. At the completion of the study (i.e., at issuance of final report), the final database will be transferred to the Sponsor.

9.8 Reference to Declaration of Helsinki/Basic Principles

The protocol will be conducted in accordance with the U.S. Code of Federal Regulations governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56), Investigational New Drug Application (21 CFR 312, Subpart D), and the Declaration of Helsinki. As such, these sections of U.S. Title 21 CFR, along with the applicable ICH Guidelines, are commonly known as Good Clinical Practices (GCPs).

10. FINAL REPORT

Upon completion of the study, a draft Study Report will be submitted to the Sponsor by Covance CRU. The report will include a summary of safety data and a summary of biomarker analysis data. The Study Report will follow the FDA ICH guidelines (or other applicable guidelines/regulations). The Covance CRU Quality Assurance Unit will perform an audit of the report.

The Sponsor will arrange with the analytical laboratories that in the analysis of samples and provision of applicable written reports/data, the analytical laboratories will comply with the applicable CAP, CLIA, and/or Good Laboratory Practices standards and with the protocol specifications.

After review by the Sponsor, a final Study Report will be submitted to the Sponsor which incorporates the Sponsor's comments.

INVESTIGATOR/SPONSOR AGREEMENT

I have read the foregoing protocol and agree to conduct the study as described herein.

Russell M. Dixon, MD
Medical Director/Principal Investigator
Covance Clinical Research Unit Inc.

April 27th 2001
Date

Roger Walk, PhD, D.A.B.T.
Director, Worldwide Scientific Affairs
Philip Morris, U.S.A.

April 30, 2001
Date

REFERENCES

[1] Source: American Cancer Society Cancer Prevention Study II

[2] Benowitz, N.L. Biomarkers of Environmental Tobacco Smoke Exposure. Environmental Health Perspectives Supplements. 1999;107(suppl 2):349-355.

[3] Michaelis, Clemens, Kijewski, Neurath, Eggert. Acetonitrile serum concentrations and cyanide blood levels in a case of suicidal oral acetonitrile ingestion. *Clin Tox.* 1991;29(4):447-458.

[4] Jordan A, Hansel A, Holzinger R, Lindinger W. Acetonitrile and benzene in the breath of smokers and non-smokers investigated by proton transfer reaction mass spectrometry (PTR-MS). *International Journal of Mass Spectrometry and Ion Processes.* 1995;148(1-2):L1-L3.

[5] Hamm S and Warneck P. Gas-chromatographic determination of acetonitrile in air using a thermionic detector. *Analytical Chem.* 1990;62 (17):1876-1883.

[6] Falter B, Kutzer C, Richter E. Biomonitoring of hemoglobin adducts: Aromatic amines and tobacco-specific nitrosamines. *Clinical Investigator.* 1994;72;364-371.

[7] Bailey AL, Wortley G, Southon S. Measurements of aldehydes in low density lipoprotein by high performance liquid chromatography. Free Radical Biology and Medicine. 1997;23(7):1078-1085.

[8] Bentley MC, Abrar M, Kelk M, Cook J, Phillips K. Validation of an assay for the determination of cotinine and 3-hydroxycotinine in human saliva using automated solid phase extraction and liquid chromatography with tandem mass spectrometric detection. *Journal of Chromatography.* 1999;723:185-194.

[9] Hecht, SS and Tricker, AR. Nitrosamines derived from nicotine and other tobacco alkaloids. In: Analytical Determination of Nicotine and Related Compounds and Their Metabolites; Gorrod, JW and Jacob, P, edit. Elsevier, 1999.

[10] Borgerding MF, Bodnar JA, and Wingate DE, comps. The 1999 Massachusetts Benchmark Study: Final Report. Boston, MA: Massachusetts Dept of Public Health; July 24, 2000.

[11] Jobson, JD. Applied Multivariate Data Analysis, Volume 1: Regression and Experimental Design. Springer-Verlag: New York, 1992.

[12] Morrison, DF. Multivariate Statistical Methods, 2nd Edition, McGraw-Hill: New York, 1976.

[13] Willers, S, Axmon, A, Feyerabend, C, Nielsen, J, Skarping, G, and Skerfving, S. Assessment of environmental tobacco smoke exposure in children with asthmatic symptoms by questionnaire and cotinine concentrations in plasma, saliva, and urine. *J Clin Epidemiol*; 2000;53:715-721.

[14] Haley, NJ, Colosimo, SG, Axelrad CM, Harris, R, and Sepkovic, DW. Biochemical validation of self-reported exposure to environmental tobacco smoke. *Environmental Research*; 1989;49:127-135.

[15] Tang, D, Warburton, D, Tannenbaum, SR, Skipper, P, Santella, RM, Cereijido, GS, Crawford, FG, and Perera, FP. Molecular and genetic damage from environmental tobacco smoke in young children. *Cancer Epidemiology, Biomarkers & Prevention*; 1999;8:427-431.

APPENDIX A – Telephone Screening Sample Questions/Procedures

When the potential subject calls the research site, the Covance screening/recruiting personnel will first allow the caller to ask questions about the study and any procedures involved. After answering any questions posed by the caller, the Covance personnel will proceed to ask a series of questions similar to, but not limited to, the following.

Are you 21 years of age or older?
If female, are you pregnant or nursing?
Do you have diabetes?
Do you have thyroid disease?
Do you have anemia or other blood diseases?
Do you have asthma, emphysema, sleep apnea, or other respiratory problems?
Do you require the use of supplemental oxygen?
Do you have high blood pressure or other heart problems?
Do you have ulcers or any other problems with your stomach or intestines?
Do you get migraines?
Do you have epilepsy or seizures?
Do you have hepatitis or other liver diseases?
Do you have kidney stones or any other kidney diseases?
Do you have a history of any psychiatric conditions, such as depression or anxiety?
Within the past year, have you received any treatment for cancer?
Have you ever had a stroke?
Within the past year, have you received any treatment for high cholesterol?
Are you HIV positive?
Have you ever tested positive for tuberculosis?
Within the past year, have you received any treatment for any allergies?
Have you ever had an abnormal electrocardiogram (ECG)?
Have you been diagnosed with alcoholism or drug addiction within the last year?
What brand(s) of cigarettes do you smoke? (Covance personnel – check list to determine eligibility.)
Have you switched your cigarette brand(s) during the last 3 months?
Have you smoked regularly at least 1 manufactured cigarette per day for the last year?
Have you smoked cigars or pipes in the last 3 months?
Have you chewed tobacco in the last 3 months?
Have you used a nicotine patch, nicotine spray, nicotine inhaler, nicotine lozenge, or nicotine gum within the last 3 months?

APPENDIX A – Telephone Screening Sample Questions/Procedures

Are you using any prescription medications?
Have you ever had difficulty getting your blood drawn?
Have you donated or received whole blood or blood products within the last 3 months?
Have you ever been or are you currently employed by the tobacco industry?
Are you or a relative employed by the tobacco industry?
Are you currently employed by a contract research organization (i.e., Covance)?
Are you or a relative employed by a contract research organization (i.e., Covance)?

APPENDIX B - Laboratory Evaluations

Chemistry[a]:	Hematology[a]:	Urine Drug Screen[a]:
Iron	White Blood Cells	Amphetamine Class
Calcium	Red Blood Cells	Amphetamine
Phosphorus	Hemoglobin	Methamphetamine (Desoxyn)
Glucose	Hematocrit	Barbiturate Class
BUN	MCV	Amobarbital (Amytal)
Creatinine	MCH	Butabarbital (Butisol)
Uric Acid	MCHC	Butalbital (Fiorinal)
Total Protein	Differential: (% & abs)	Pentobarbital (Nembutal)
Albumin	Neutrophils	Phenobarbital (Luminal)
Total Bilirubin	Lymphocytes	Secobarbital (Seconal)
Alkaline Phosphatase	Monocytes	Narcotic Class
LDH	Eosinophils	Codeine
AST (SGOT)	Basophils	Dihydrocodeine
ALT (SGPT)	Platelets (quantitative)	Hydrocodone
Sodium	RBC morphology	Hydromorphone (Dilaudid)
Potassium		Methadone
Chloride		Morphine
Cholesterol		Norpropoxyphene (Darvon)
Triglycerides		Oxycodone
	Other:	Propoxyphene (Darvon)
	HBsAg[b]	Meperidine (Demerol)
	Anti-HCV[b]	Pentazocine (Talwin)
Urinalysis[a]:	HIV Antibody[b]	Miscellaneous Agents
Color		Cocaine and/or Metabolite(s)
pH & Specific Gravity		Phencyclidine (PCP)
Glucose Protein		Cannabinoids (THC)
Ketones Nitrite		
Urobilinogen Bilirubin		
Leukocytes Occult Blood		
Microscopic (including RBCs and WBCs per HPF)		

[a]Obtained at screening and enrollment only.
[b]Obtained at each site visit.

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

A. Urine Samples for Phenotyping CYP1A2 and NAT2

1. At the time of enrollment after collection of any other blood/urine samples, the subjects will be given a dose of approximately 200 mg of caffeine (No-Doz®, 1 caplet).
2. Approximately 4 to 5 hours after administration of the caffeine dose, a urine sample will be collected from the subjects.
3. Remove 1 aliquot of 10-mL and place into appropriately-labeled, polypropylene screwcap tubes containing 200 mg ascorbic acid and place into a freezer set to maintain a temperature of approximately –20°C for storage prior to shipment.
4. Ship the urine samples (using a sufficient supply of dry ice to maintain frozen state) for distribution to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)

   On the day of shipment, Covance CRU staff will notify (via telephone) the Central Laboratory Service of the pending shipment.
5. Urine samples for analysis of caffeine and caffeine metabolites will be distributed to:

   Covance Laboratories Inc.
   3301 Kinsman Boulevard
   Madison, Wisconsin 53704
   Contact Person: Bonnie Walke
   608-242-2734 (Main Office Telephone No.)
   608-242-2732 (Main Office Facsimile No.)
6. The data obtained from the testing will be returned to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)
7. In turn, Covance Central Laboratory Services will provide the database for complete analysis to:

   Covance Clinical Research Unit, Inc.
   309 West Washington Avenue, Suite Four East
   Madison, Wisconsin 53703
   608-283-6060 (Main Office Telephone No.)
   608-283-5697 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

B. Whole Blood Samples for Assessment of Acetonitrile

1. At the time of sample collection: collect 1 whole blood sample using a 6-mL collection tube containing K_3EDTA. Immediately following collection, gently invert blood samples and place on ice.
2. Transfer the contents of the 6-mL tube to an appropriately labeled polypropylene screwcap tube and place into a freezer set to maintain a temperature of approximately -20°C or lower for storage prior to shipment. These whole blood samples are to be used for acetonitrile analysis.
3. Ship the whole blood samples (using a sufficient supply of dry ice to maintain frozen state) for distribution to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)

   On the day of shipment, Covance CRU staff will notify (via telephone) the Central Laboratory Service of the pending shipment.
4. Whole blood samples for analysis of acetonitrile will be distributed to:

   Covance Madison West
   802 Deming Way
   Madison, Wisconsin 53717
   Contact Person: Diane Green
   608-664-3040 (Main Office Telephone No.)
   608-664-3022 (Main Office Facsimile No.)
5. The data obtained from the testing will be returned to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)
6. In turn, Covance Central Laboratory Services will provide the database for complete analysis to:

   Covance Clinical Research Unit, Inc.
   309 West Washington Avenue, Suite Four East
   Madison, Wisconsin 53703
   608-283-6060 (Main Office Telephone No.)
   608-283-5697 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

C. Blood Sample Collection to Obtain Plasma for Assessment of Malondialdehyde and RBCs for Assessment of 3- and 4-Aminobiphenyl Hemoglobin Adducts

1. At the time of sample collection: collect 2 whole blood samples using 10-mL collection tubes containing K$_2$EDTA. Immediately following collection, gently invert blood samples and place on ice. NOTE: For the Week 3 collection, the RBC pellets for hemoglobin adduct analysis are not required. Only the plasma for malondialdehyde analysis will be collected/shipped.
2. Within 60 minutes of the collection timepoint, centrifuge the tubes at approximately 3,000 x G for 10 minutes at approximately 5°C to separate the red blood cells. Transfer 4 aliquots of the plasma (approximately 1.5 mL per aliquot) into appropriately-labeled 2-mL polypropylene screwcap tubes and place into a freezer set to maintain a temperature of –20°C or lower for storage prior to shipment. These aliquots are to be used for malondialdehyde analysis.
3. The resulting RBC pellets in the tubes will be washed with 3 portions of 0.9% sterile saline (volume of saline solution approximately equal to the volume of plasma removed from the tube; mix by gentle inversion, centrifuge [3,000 x G for 10 minutes at approximately 5°C], remove and discard wash solution) and the resulting RBC pellet will be placed into conical bottomed, screwcap polypropylene tube. The samples will be placed into a freezer set to maintain a temperature of –20°C or lower for storage prior to shipment. These RBC pellets are to be used for analysis of 3- and 4-aminobiphenyl hemoglobin adducts.
4. Ship the plasma and RBC samples (using a sufficient supply of dry ice to maintain frozen state) for distribution to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)

   On the day of shipment, Covance CRU staff will notify (via telephone) the Central Laboratory Service of the pending shipment.

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

C. Blood Sample Collection to Obtain Plasma for Assessment of Malondialdehyde and RBCs for Assessment of 3- and 4-Aminobiphenyl Hemoglobin Adducts

5a. Plasma samples for analysis of malondialdehyde will be distributed to the following laboratories (2 aliquots to each laboratory):

Covance Laboratories Ltd.
Otley Road
Harrogate
North Yorkshire
HG3 1PY England
Contact Person: Christine Norton
44-1423-566-558 (Main Office Telephone No.)
44-1423-569-595 (Main Office Facsimile No.)

(A subset of samples corresponding to 12% of subjects' samples [4 subjects from each subgroup] will be sent to:)

University of Texas Southwestern Medical Center
Center for Human Nutrition
Clinical Chemistry Department
Dallas, Texas 75390-9073
Contact Person: Dr. Sridevi Devaraj
214-648-2766 (Main Office Telephone No.)
214-648-8037 (Main Office Facsimile No.)

5b. Washed, packed red blood cells for analysis of 3- and 4-aminobiphenyl hemoglobin adducts will be distributed to the following analytical laboratories:

Covance Laboratories Ltd.
Otley Road
Harrogate
North Yorkshire
HG3 1PY England
Contact Person: Christine Norton
44-1423-566-558 (Main Office Telephone No.)
44-1423-569-595 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

C. Blood Sample Collection to Obtain Plasma for Assessment of Malondialdehyde and RBCs for Assessment of 3- and 4-Aminobiphenyl Hemoglobin Adducts

5b. Washed, packed red blood cells for analysis of 3- and 4-aminobiphenyl hemoglobin adducts will be distributed to the following analytical laboratories:

(A subset of samples corresponding to 12% of subjects' samples [4 subjects from each subgroup] will be sent to:)

INBIFO GmbH
Fuggerstr. 3
D-51149 Cologne
Germany
Contact Person: Dr. Georg Schepers
49-2203-3031 (Main Office Telephone No.)
49-2203-303-362 (Main Office Facsimile No.)

On the day of shipment, Covance Central Laboratories staff will notify (via telephone) each respective laboratory of the pending shipment. The shipment will contain full documentation of the samples sent and shipment will only be made on Monday through Wednesday.

6. The results of the tests conducted at University of Texas Southwestern Medical Center and INBIFO will be provided to Covance Laboratories – Harrogate. The complete set of results for both malondialdehyde and 3- and 4-aminobiphenyl tests will be returned to:

Covance Central Laboratory Services
8211 Scicor Drive
Indianapolis, Indiana 46214
317-271-1200 (Main Office Telephone No.)
317-273-4030 (Main Office Facsimile No.)

7. In turn, Covance Central Laboratory Services will provide the database for complete analysis to:

Covance Clinical Research Unit, Inc.
309 West Washington Avenue, Suite Four East
Madison, Wisconsin 53703
608-283-6060 (Main Office Telephone No.)
608-283-5697 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

D. Whole Blood Sample for Assessment of Carboxyhemoglobin

1. At the time of sample collections after enrollment, collect a single 3-mL collection tube containing K_3EDTA for carboxyhemoglobin analysis.
2. Immediately following collection, gently invert blood samples. Do not expose the tube contents to the environment.
3. Ship whole blood samples for analysis (at ambient temperature) to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)

   On the day of shipment, Covance CRU staff will notify (via telephone) Covance Central Laboratory Services of the pending shipment.
4. The data obtained from the testing of the samples will be stored in a database. Covance Central Laboratory Services will provide the database for complete analysis to:

   Covance Clinical Research Unit, Inc.
   309 West Washington Avenue, Suite Four East
   Madison, Wisconsin 53703
   608-283-6060 (Main Office Telephone No.)
   608-283-5697 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

E. Blood Sample Collection to Obtain Plasma Sample for Assessment of Fibrinogen

1. At the time of sample collections after enrollment, collect a single 2.7-mL citrate tube.
2. Immediately following collection, gently invert blood samples and place on ice.
3. Within 60 minutes of collection, centrifuge the citrate tube at approximately 1,500 x G for approximately 15 minutes at approximately 5°C. Transfer the plasma aliquot, using standard laboratory technique, into an appropriately labeled storage tube and store in a freezer set to maintain a temperature of –20°C or lower until shipped on the same day.
4. Ship plasma sample for analysis of fibrinogen (with sufficient dry ice to maintain frozen state) to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)

   On the day of shipment, Covance CRU staff will notify (via telephone) Covance Central Laboratory Services of the pending shipment.
5. The data obtained from the testing of the samples will be stored in a database. Covance Central Laboratory Services will provide the database for complete analysis to:

   Covance Clinical Research Unit, Inc.
   309 West Washington Avenue, Suite Four East
   Madison, Wisconsin 53703
   608-283-6060 (Main Office Telephone No.)
   608-283-5697 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

F. Blood Sample Collection to Obtain Serum Samples for Assessment of C-Reactive Protein, HDL-cholesterol, LDL-cholesterol, and HIV and Hepatitis Screens:

1. At the time of sample collections after enrollment, collect a total of 3 tubes of blood as follows:
   - A single 5 mL serum separator tube for C-reactive protein, HDL-cholesterol, and LDL-cholesterol analysis;
   - A single 9 mL serum separator tube for HIV and hepatitis screens.
2. Immediately following collection, gently invert blood samples.
3. Within 60 minutes of collection, centrifuge the tubes at approximately 1,500 x G for approximately 15 minutes at ambient temperature. Transfer serum aliquots, using standard laboratory technique, into appropriately-labeled storage tubes and store the serum for analysis of C-reactive protein, HDL-cholesterol, and LDL-cholesterol, the HIV and hepatitis screens at ambient temperature until shipped.
4. Ship serum sample for analysis of C-reactive protein, HDL-cholesterol, LDL-cholesterol, and screens for HIV and hepatitis antibodies (all at ambient temperature) to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)

   On the day of shipment, Covance CRU staff will notify (via telephone) Covance Central Laboratory Services of the pending shipment.
5. The data obtained from the testing of the samples will be stored in a database. Covance Central Laboratory Services will provide the database for complete analysis to:

   Covance Clinical Research Unit, Inc.
   309 West Washington Avenue, Suite Four East
   Madison, Wisconsin 53703
   608-283-6060 (Main Office Telephone No.)
   608-283-5697 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

G. Urine Samples for Assessment of 11-Dehydro-thromboxane B_2 and 8-Epi-$PGF_{2\alpha}$:

1. Supply each subject with a smaller collection container and a plastic ziplock bag into which to place the smaller container for storage in the freezer.
2. Instruct the subject to collect a void into the smaller collection container upon waking the day of their scheduled appointment and freeze it after collection. This "first void" will be used for analysis of 11-dehydro-thromboxane B_2 and 8-epi-$PGF_{2\alpha}$ analyses. The analyses of these samples will also include a determination of creatinine levels.
3. When the subject returns the urine samples, remove 4 aliquots of approximately 5 mL each and place into appropriately labeled polypropylene screwcap tubes.
4. Store the urine aliquots upright in a freezer set to maintain a temperature of approximately -20°C or lower.
5. The urine aliquots for analysis of 11-dehydro-thromboxane B_2 and 8-epi-$PGF_{2\alpha}$ (and creatinine) will be sent for further distribution to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)

   On the day of shipment, Covance CRU staff will notify (via telephone) the Central Laboratory Service of the pending shipment.
6. The urine samples will be distributed to the following analytical laboratories:

   Covance Laboratories Ltd.
   Otley Road
   Harrogate
   North Yorkshire
   HG3 1PY England
   Contact Person: Christine Norton
   44-1423-566-558 (Main Office Telephone No.)
   44-1423-569-595 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

G. Urine Samples for Assessment of 11-Dehydro-thromboxane B_2 and 8-Epi-$PGF_{2\alpha}$:

7. The data obtained from the testing of the samples will be returned to:

Covance Central Laboratories
8211 Scicor Drive
Indianapolis, Indiana 46214
317-271-1200 (Main Office Telephone No.)
317-273-4030 (Main Office Facsimile No.)

8. In turn, Covance Central Laboratories will provide the database for complete analysis to:

Covance Clinical Research Unit, Inc.
309 West Washington Avenue, Suite Four East
Madison, Wisconsin 53703
608-283-6060 (Main Office Telephone No.)
608-283-5697 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

H. Urine Samples for Assessment of Nicotine and Nicotine Metabolites, NNAL and NNAL-Glucuronide, and Malondialdehyde

1. Supply each subject with a urine collection device, a large urine collection container, and a cooler in which to store the urinal and large urine containers. Further instructions will contain details to collect urine voids into the urinal and to transfer all voids into the large urine collection container during the 24-hour collection periods.
2. Within 60 minutes after the subject returns the large urine collection container, measure and record the total volume of the urine.

3a. After obtaining the volume, remove 4 aliquots of approximately 5 mL each and place them into separate, appropriately-labeled polypropylene tubes (for nicotine and nicotine metabolite analyses).

3b. Remove 2 aliquots of approximately 4 mL of urine and place them into separate, appropriately labeled polypropylene containers (for malondialdehyde analyses).

3c. Remove 7 aliquots of approximately 100 mL of urine and place them into separate, appropriately labeled polypropylene containers (for NNAL and NNAL-glucuronide analyses).

4. Store the urine aliquots upright in a freezer set to maintain a temperature of approximately -20°C. An aliquot (approximately 200 mL, or the remaining volume if less than 200 mL) of the remaining "bulk" urine will be removed and retained by Covance Central Laboratory Services for possible further testing.
5. All urine aliquots/samples will be sent for further distribution to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)

   On the day of shipment, Covance CRU staff will notify (via telephone) the Central Laboratory Service of the pending shipment.

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

H. Urine Samples for Assessment of Nicotine and Nicotine Metabolites, NNAL and NNAL-Glucuronide, and Malondialdehyde

6. The urine samples for analysis of nicotine and nicotine metabolites will be distributed to the following analytical laboratories (2 aliquots to each laboratory):

Covance Laboratories Ltd.
Otley Road
Harrogate
North Yorkshire
HG3 1PY England
Contact Person: Christine Norton
44-1423-566-558 (Main Office Telephone No.)
44-1423-569-595 (Main Office Facsimile No.)

(A subset of samples corresponding to 12% of subjects' samples [4 subjects from each subgroup] will be sent to:)

INBIFO GmbH
Fuggerstrasse 3
D-51149 Cologne
Germany
Contact Person: Dr. Georg Schepers
49-2203-3031 (Main Office Telephone Number)
49-2203-303-362 (Main Office Facsimile Number)

7. The urine samples for analysis of NNAL and NNAL-glucuronide will be distributed to the following analytical laboratories.

5 Aliquots sent to: Covance Laboratories Inc.
3301 Kinsman Boulevard
Madison, Wisconsin 53704
Contact Person: Bonnie Walke
608-242-2734 (Main Office Telephone No.)
608-242-2732 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

H. Urine Samples for Assessment of Nicotine and Nicotine Metabolites, NNAL and NNAL-Glucuronide, and Malondialdehyde

7. The urine samples for analysis of NNAL and NNAL-glucuronide will be distributed to the following analytical laboratories.

(A subset of samples corresponding to 12% of subjects' samples [4 subjects from each subgroup] will be sent to:)

2 Aliquots sent to: INBIFO GmbH
Fuggerstrasse 3
D-51149 Cologne
Germany
Contact Person: Dr. Georg Schepers
49-2203-3031 (Main Office Telephone Number)
49-2203-303-362 (Main Office Facsimile Number)

8. The urine samples for analysis of malondialdehyde will be distributed to the following analytical laboratories (2 aliquots to each laboratory):

Covance Laboratories Ltd.
Otley Road
Harrogate
North Yorkshire
HG3 1PY England
Contact Person: Christine Norton
44-1423-566-558 (Main Office Telephone No.)
44-1423-569-595 (Main Office Facsimile No.)

(A subset of samples corresponding to 12% of subjects' samples [4 subjects from each subgroup] will be sent to:)

University of Texas Southwestern Medical Center
Center for Human Nutrition
Clinical Chemistry Department
Dallas, Texas 75390-9073
Contact Person: Dr. Sridevi Devaraj
214-648-2766 (Main Office Telephone No.)
214-648-8037 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

H. Urine Samples for Assessment of Nicotine and Nicotine Metabolites, NNAL and NNAL-Glucuronide, and Malondialdehyde

9. The results of the tests conducted at University of Texas Southwestern Medical Center and INBIFO will be provided to Covance Laboratories – Harrogate. The complete set of results for both malondialdehyde and nicotine and nicotine metabolite tests will be returned to:

Covance Central Laboratories
8211 Scicor Drive
Indianapolis, Indiana 46214
317-271-1200 (Main Office Telephone No.)
317-273-4030 (Main Office Facsimile No.)

10. In turn, Covance Central Laboratories will provide the database for complete analysis to:

Covance Clinical Research Unit, Inc.
309 West Washington Avenue, Suite Four East
Madison, Wisconsin 53703
608-283-6060 (Main Office Telephone No.)
608-283-5697 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

I. Exhalate Sample Collection for Analysis of Acetonitrile

1. Within 30 minutes of the subjects reporting to the research site, an exhalate sample will be collected. Prior to the CO monitoring or the collection of exhalate samples, the smoking subjects will be queried about the time of their last cigarette.
2. The subjects will be asked to inhale deeply and to hold for 20 seconds (similar to CO monitor instructions).
3. The subjects will then be given a tube leading to a Tedlar® bag. They will be instructed to exhale slowly and steadily until the bag is full or until they have fully exhaled.
4. The bags will be sealed immediately after collection to minimize the mixing effect with environmental air. Site personnel will process the exhalate to transfer the exhaled air onto thermal desorption tubes using air sampling pumps. The thermal desorption tubes will be stored at –20°C or below prior to shipping.
5. The tubes will then be sent for further distribution to::

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)

   On the day of shipment, Covance CRU staff will notify (via telephone) the Central Laboratory Service of the pending shipment.
6. The tubes for analysis of acetonitrile in exhalate will be distributed to the following analytical laboratory:

   Covance Madison West
   802 Deming Way
   Madison, Wisconsin 53717
   Contact Person: Diane Green
   608-664-3030 (Main Office Telephone No.)
   608-664-3022 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

I. Exhalate Sample Collection for Analysis of Acetonitrile

7. The data obtained from the testing of the samples will be returned to:

Covance Central Laboratories
8211 Scicor Drive
Indianapolis, Indiana 46214
317-271-1200 (Main Office Telephone No.)
317-273-4030 (Main Office Facsimile No.)

8. In turn, Covance Central Laboratories will provide the database for complete analysis to:

Covance Clinical Research Unit, Inc.
309 West Washington Avenue, Suite Four East
Madison, Wisconsin 53703
608-283-6060 (Main Office Telephone No.)
608-283-5697 (Main Office Facsimile No.)

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

J. Carbon Monoxide Measurements in Exhalate

Within 30 minutes of arrival at the research site, the subjects will be asked to undergo a measurement of carbon monoxide in their exhaled breath. The procedure will be performed at site visits during Weeks 1, 2, 3, and 6. Numerical results will be recorded in the subject's respective CRF.

(Excerpted from Micro Medical MicroCO Meter Operating Manual)

For accurate results, the CO meter should be used at room temperature. Insert the mouthpiece adapter into the MicroCO meter and then insert a disposable mouthpiece into the adapter. Turn the unit on by selecting the upper (%COHb) or middle (CO) position on the central slide switch. The display should show:

This will appear momentarily while the correction for ambient levels of CO is executed. During this time, do not expose the unit to raised levels of CO. A buzzer or beep will sound and the display will change to:

Upon hearing the buzzer/beep, the subject will be instructed to take a full, deep breath and hold it. The display will count down from 20 to 0 as an aid to time the breath holding time. This holding time is to allow for equilibration of alveolar gases. If the subject is unable to hold his/her breath for this period, the unit may be used before the 20 second time elapses. A green indicator light will illuminate and the display will change to:

At this prompt, the subject should be instructed to seal their mouth around the mouthpiece and exhale slowly and fully. The display will show a series of rising numbers over the course of several seconds. The final value will be held until the unit is turned off and it represents the parts per million of CO (or %COHb depending on the switch position).

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

J. Carbon Monoxide Measurements in Exhalate

Before repeating a measurement or between subjects, the unit must be turned off and the mouthpiece and adapter removed for at least 1 minute. Before using for another subject, visually inspect the unit to ensure that all moisture has evaporated from the surface of the sensor.

If the unit is turned on too quickly after use, there is a possibility that residual expired carbon monoxide may still be present. If that occurs, the display will show:

If the display shows this, turn the unit off, remove the mouthpiece and adapter, and expose to ambient air for 2 minutes before trying again.

APPENDIX C - Sample Collection, Processing, Storage, and Shipment

K. Spontaneous Sputum Samples:

1. Subjects will be given an appropriate collection vessel (e.g., sterile cup or 50 mL conical tube) in which to collect a spontaneous sputum sample on the day of each site visit (i.e., they will be given the collection vessel at the prior weeks visit for the following scheduled visit). They will be asked to produce a sample, if possible, and to store it refrigerated/cooled until return to the research site.
2. Also, at any time during the site visits if a subject produces (and is willing to relinquish) a spontaneous sputum sample, the sample will be collected into a sterile cup or conical tube.
3. The sputum sample will be returned to the site (or if at the site, given to site personnel) and stored in a freezer set to maintain approximately –20°C or lower until shipment.
4. Any sputum samples will be sent to, and stored (for possible further testing) until the end of the study at:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)

APPENDIX C – Sample Collection, Processing, Storage, and Shipment

L. Cigarette Butt Collection Procedure

1. During Weeks 1, 2, 3, and 6, smoking subjects will be instructed to collect the butt (i.e., filter and any remaining cigarette portion) of all cigarettes smoked during the durations of the urine collections. The cigarette butts will be placed into a HDPE container supplied by the research site that is labeled with each respective subject's number, protocol number, and week of collection (i.e., Week 1, Week 2, or Week 3). The subject's instructions will include the following:
   - Please extinguish the cigarettes thoroughly before placing into container.
   - Remove cover of container and place thoroughly-extinguished cigarette into the container.
   - Replace cover on container and tighten.
   - Store container at room temperature until returned to research site.
2. The returned cigarette butts will be counted at the research site and the count will be recorded.
3. Collected cigarette butts will be sent at ambient temperature for further distribution to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)
4. The containers will be distributed to:

   INBIFO GmbH.
   Fuggerstrasse 3
   D-51149 Cologne
   Germany
   Attn: Dr. Georg Schepers
   011-49-[redacted])
   [redacted])

APPENDIX C – Sample Collection, Processing, Storage, and Shipment

L. Cigarette Butt Collection Procedure

5. The data obtained from the testing of the samples will be provided to Covance Laboratories – Harrogate and will, in turn, be sent to:

   Covance Central Laboratory Services
   8211 Scicor Drive
   Indianapolis, Indiana 46214
   317-271-1200 (Main Office Telephone No.)
   317-273-4030 (Main Office Facsimile No.)

6. In turn, Covance Central Laboratories will provide the database for complete analysis to:

   Covance Clinical Research Unit, Inc.
   309 West Washington Avenue, Suite Four East
   Madison, Wisconsin 53703
   608-283-6060 (Main Office Telephone No.)
   608-283-5697 (Main Office Facsimile No.)

APPENDIX C – Sample Collection, Processing, Storage, and Shipment

M. Cigarette Pack Collection Procedure

1. During Weeks 1, 2, 3, and 6, smoking subjects will be instructed to collect the pack from which the collected cigarette butts were removed from during the durations of the urine collections. The cigarette packs will be placed into a ziplock type bag supplied by the research site that is labeled with each respective subject's number, protocol number, and week of collection.
2. When the smoking subjects return to the research site, the packs will be collected and checked against the cigarette collections. Any discrepancies between the packs and butts will be noted (i.e., the butts will be counted and divided by 20 [the number of cigarettes per pack] and the approximate number of packs will be determined; the count of the packs will include any partial packs that the subject returns).
3. All packs that are returned to the research site (including the partial packs) will be photocopied along with the collection bag (contains the subject number, week number, protocol number). Any partial packs with which the subject reports to the site will be returned to the subject prior to the end of the visit.
4. After obtaining the photocopies of the packs, the empty packs will be discarded.

APPENDIX D – Elements to be Included in Informed Consent Form

Informed consent must be obtained from every subject before he/she enters the study. It must be given freely and not under duress. Consent must be documented by the subject signing an IRB-approved consent form. A copy of the signed consent form must be given to the subject signing it. Another copy must be kept in the Investigator's files and made available to Sponsor and any regulatory agency representatives upon request. Before the study begins, a sample of the consent form must be provided to the Sponsor.

Basic Elements of Informed Consent

Every consent form must include the following 8 elements:

- A statement that the study involves research, an explanation of the purpose of the research, and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of procedures that are experimental;
- A description of any reasonably foreseeable risks or discomforts to the subject;
- A description of any benefits to the subject or to others that may reasonably be expected from the research;
- A disclosure of appropriate alternative procedures or course of treatment, if any, that might be advantageous to the subject;
- A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that a regulatory agency (e.g., FDA) may inspect the records;
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

APPENDIX D – Elements to be Included in Informed Consent Form

- An explanation of whom to contact for answers to pertinent questions about the research and the research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subjects is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information will also be included in the consent form:

- Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the subject's consent;
- Any additional costs the subject may incur from participation in the research;
- The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
- A statement that significant new findings developed during the course of the research that may relate to the subject' willingness to continue participation will be provided to the subject; and
- The approximate number of subjects involved in the study.

APPENDIX E – Interviewer Instructions, Questionnaire, and Weekly Surveys

Note that the questionnaire and weekly survey contained herein is the interviewer copy. References to "skips" and other interviewer instructions will not be included in the hard copy referenced by the subjects.

Interviewer's Instructions

Protocol No. PM-8450 Covance Study No. 12226-8450

General Instructions for the Interviewer

How do I dress?
Wear business casual clothes, no jeans or t-shirts.

How long will each questionnaire take?
The questionnaire should take around 30 minutes. The weekly survey will take about 20 minutes. Let the subject know this before you begin the interview.

Are any breaks allowed?
Subjects can stop the interview at any time for smoking or bathroom breaks.

How do I prepare for the interview?
Read the questionnaire, weekly survey, and these guidelines several times.
Practice the interview several times with another employee as the subject. Make sure that you really understand the questions you are asking.
Pay attention to your body language. Do you appear interested or bored? Are you slouching? Are you making eye contact?
Pay attention to how you ask the questions. Is your tone monotonous? Are you speaking clearly and loudly enough?
Ask your practice partner for honest feedback on how you are presenting yourself.

How do I develop a rapport with the subject?
Introduce yourself.
Remain unbiased and impartial.
Speak clearly in a calm and unflustered manner.
Do not express either negative or positive feelings.
Reinforce the subject's responses with verbal cues such as repeating the subject's answer.

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APPENDIX E – Interviewer Instructions, Questionnaire, and Weekly Surveys

Interviewer's Instructions

How do I ask the questions?
Ask the questions exactly as they are worded.
Do not omit questions you think are answered by other questions.
Ask the questions in the order in which they are presented.
Ask every question specified.
Read each question slowly.
Repeat questions that are misunderstood or misinterpreted.
Do not let the subject stray from the questions in the interview.
Keep nonverbal cues as neutral as possible.
It is not necessary to read the "skip" references aloud with the question.
Special introductions/clarifications for certain sections are provided in ***bolded italics*** text; those should be read aloud as well.

How do I record the Subject's responses?
Enter the subject's responses directly into the computer.
Repeat the subject's responses to verify them.

Does the subject understand?
Know what an adequate answer to each question is.
Indications that the subject does not understand a question include:

- Not answering.
- Providing an answer that seems inconsistent or wrong.

What can I do to help the subject understand?
Use a probing technique such as:

- Repeat the question.
- Give an expectant pause.
- Repeat the subject's reply.
- Refer to additional clarifications for that specific question in the following specific guidelines or by selecting "help" on the computer.

When the subject seems to have difficulty with a question, insert a comment in the computer "Interviewer Comments" indicating what part of the question was troublesome.

APPENDIX E – Interviewer Instructions, Questionnaire, and Weekly Surveys

Interviewer's Instructions

Protocol No. PM-8450 Covance Study No. 12226-8450

What if the subject refuses to answer a question or cannot answer it?
For refusals, remind the subject that all responses are held in confidence and they will only be identified with a subject number in any reports of this data.
If the subject still refuses to answer a question, select "Refused/Cannot answer" in the computer for that question, insert any comments in the "Interviewer Comments" section, and move on to the next question. Do not imply the "refused" response as a possible option for all the questions, but accept it as a response for some questions if requested *specifically by the subject.*

If the subject cannot answer a question (for example, it is unclear even with the help suggestions or the correct response is not available), select "Refused/Cannot answer" insert the reason into the "Interviewer Comments," and move to the next question.

Do not rephrase or add new questions. Be careful not to add verbal emphasis on certain words or phrases. Refer to the following pages or the "help" button available with each question for what clarity may be given to specific questions as needed. Do not deviate from these guidelines by providing your personal interpretation on what you think the question means.

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APPENDIX E – Interviewer Instructions, Questionnaire, and Weekly Surveys

Interviewer's Instructions

Instructions for the Interviewer to clarify specific questions on the Questionnaire

The Interviewer is not to deviate from the clarifications given in this document or on the computer "help" button for individual questions. If the subject is confused about how to answer a question, you can refer to these guidelines for that particular question, but do not provide your personal interpretation of the question. Some of the questions are intentionally vague to allow for the subject's personal interpretation and perception. If there are no guidelines given for a particular question, you can repeat the question slowly to encourage the subject's response. These guides are not to be shown to the subject, but to serve as clarification for the Interviewer.

A hard copy of the questionnaire will be given to the subject to follow along with during the interview. A hard copy of the questionnaire will also be available to you, the Interviewer, along with these guidelines. Your copy of the questionnaire will include "skip to" references that will be removed from the subject's copy. Some questions may be skipped based on the subject's response to a previous question. For example, if the subject is not employed, he/she will not be asked the additional questions pertaining to his/her employment. The subject should not see the computer screen or your version of the hard copy of the questionnaire.

For questions requiring a numerical response, the computer will not allow you to enter a range. You must enter a specific number. The only questions allowing a range will be those where each range is given as a specific possible checkbox. If the subject provides a range, ask him/her to give one number, the subject's best estimate. Questions that ask for a number of hours should be given to the nearest half-hour.

At the beginning of the questionnaire you will ask the subject whether he/she smokes or uses certain items. The computer will automatically skip the questions/sections that are not applicable to the non-smoker. The computer will also automatically skip other non-applicable questions based on subject's answers to related questions (i.e., if the subject has never smoked a different brand, he/she will not be asked to describe the other brand he/she smoked). The hard copy of the questionnaire will contain all the questions, whether to be skipped or not, and you may have to guide the subject to the next applicable question (use page numbers and question numbers to guide the subject).

Sections and some groups of questions are prefaced with introductory comments/clarifications. Be sure to read these aloud to the subject as well. When

APPENDIX E – Interviewer Instructions, Questionnaire, and Weekly Surveys

Interviewer's Instructions

skipping non-applicable questions, these introductory statements should still be read prior to the question to which you are skipping. For example, if your answer to Question 2.1 prompts you to skip to Question 2.3 and there is an introductory statement appearing before Question 2.3, be sure not to skip the introductory statement that appears before the question when you skip Question 2.2. The computer should automatically take you to the applicable introductory comments.

Some portions of the questionnaire may also be repeated several times depending on an answer to a previous question (for example, questions about employment will be repeated for every job the subject has held in the last 3 months). The computer will automatically repeat the questions as appropriate, but you will need to guide the subject through the repeats on his/her hard copy of the questionnaire. You will also need to keep the subject thinking of the same job/person/vehicle/place through the same series of the repeated questions. The computer questions will assist you with prompts. For example, where "this job" is indicated in the hard copy, the computer may insert "this first job" for the first round, "this second job" for the second series, etc.

Some of the questions contain references to a previous question and the response from the subject in that prior question. In those cases the computer will automatically fill in the subject's response from the indicated question on the computer-generated question. The hard copy will contain a reference to the item in all capital letters and the question number to which it refers. For example, where the questionnaire reads "PREFERRED BRAND" on the hard copy, the computer-generated question will fill in the subject's specific preferred brand as provided as a response to an earlier question. If the subject's preferred brand is "X," the computer-generated question will read "How long have you been smoking X?" instead of "How long have you been smoking PREFERRED BRAND (from Question x.x)?" as the hard copy will read.

The computer will not accept an inappropriate or impossible response. If, for example, the subject states they were exposed to tobacco smoke for 25 hours per day on average, the computer would not accept that response.

The subject is allowed to go back to a question and change his/her response within the interview. Once the interview is over, there will be no changes.

The questionnaire will be timed by the computer starting after you enter a response to the first question and stopping when you have answered the last question. Once the

APPENDIX E – Interviewer Instructions, Questionnaire, and Weekly Surveys

Interviewer's Instructions

questionnaire is complete, thank the subject for his/her answers, print a hard copy of his/her answers, log off as instructed, and pick up and file the hard copy.

NOTE: Because these guidelines are meant to be read aloud to the subject, they are written in the second person to be addressed to the subject. "You" and "your" refers to the subject. There are a few "FOR INTERVIEWER ONLY" portions in these guidelines that should not be read aloud to the subject. You can read the "helps" for specific questions aloud to the subject, but do not show the subject a hard copy or the computer screen.

APPENDIX E – Interviewer Instructions, Questionnaire, and Weekly Surveys

Questionnaire

Protocol No. PM-8450 Covance Study No. 12226-8450

For Enrollment and Week 6
Version 1.1

This will be an interviewer-administered interview. The responses will be entered directly into the computer. The interview is divided into 8 sections:

- Introductory Section (answered by all subjects)
- Section 1: Demographics (answered by all subjects)
- Section 2: Employment (answered by all subjects)
- Section 3: Smoking (non-smokers skip this section)
- Section 4: Exposure to tobacco smoke of others (answered by all subjects)
- Section 5: Household exposures (answered by all subjects)
- Section 6: Alcohol use (answered by all subjects)
- Section 7: Physical Activity (answered by all subjects)
- Section 8: Nutrition (answered by all subjects)

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APPENDIX E – Interviewer Instructions, Questionnaire, and Weekly Surveys

Questionnaire

Protocol No. PM-8450 Covance Study No. 12226-8450

First, I am going to ask you some introductory questions. For each one, I will read all possible answers.

INTRODUCTORY QUESTIONS

A.1 **In the past 12 months, have you smoked any of the following?** *(Select "Yes" or "No" for each product.)*

Manufactured Cigarettes	☐ Yes	☐ No
Cigars	☐ Yes	☐ No
Cigarillos	☐ Yes	☐ No
Pipe	☐ Yes	☐ No
Other, *specify:* _____	☐ Yes	☐ No

(For example, Roll-your-own cigarettes or bidis.)

A.2 **In the past 12 months have you used any of the following nicotine-containing products?** *(Select "Yes" or "No" for each product.)*

Snuff	☐ Yes	☐ No
Chewing tobacco	☐ Yes	☐ No
Nicotine gum or lozenges (*e.g., Nicorette*)	☐ Yes	☐ No
Nicotine inhalers (*e.g., Nicotrol Nasal Spray*)	☐ Yes	☐ No
Nicotine patches (*e.g., Nicorette Patch*)	☐ Yes	☐ No
Nicotine sprays (*e.g., Nicotrol Inhaler*)	☐ Yes	☐ No
Other, *specify:* _____	☐ Yes	☐ No

A.3 **Have you <u>ever</u> smoked manufactured cigarettes on a <u>regular</u> basis? That is, have you ever smoked at least 1 manufactured cigarette per day for a year?**

☐ Yes
☐ No

IF "NO" TO "MANUFACTURED CIGARETTES" IN QUESTION A.1, SKIP SECTION 3.

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Now, I am going to ask you some questions for classification purposes. Some of the answers would appear to be obvious to me, but I still need to ask you each of these questions. For each one, I will read all possible answers.

SECTION 1
DEMOGRAPHICS

1.1 **What is your gender?**
- ☐ Male
- ☐ Female

1.2 **Are you Spanish/Hispanic/Latino?**
- ☐ Yes
- ☐ No

1.3 **What is your race?**
- ☐ Asian
- ☐ African American/Black
- ☐ Caucasian
- ☐ Native American
- ☐ Other, *specify:*_____

1.4 **What is your current marital status?**
- ☐ Married
- ☐ Divorced
- ☐ Widowed
- ☐ Separated
- ☐ Never been married

1.5 **What is the highest grade or level of schooling you completed?**
- ☐ Never attended school
- ☐ Completed a grade between kindergarten and 8th grade (middle school)
- ☐ Completed a grade between 9th and 11th grade (some high school)
- ☐ Completed 12th grade or a GED (high school graduate)
- ☐ Attended some technical/vocational/trade school, but did not complete
- ☐ Completed technical/vocational/trade school
- ☐ Attended some college but did not get a degree
- ☐ Completed undergraduate Bachelor's degree
- ☐ Completed additional post-graduate education

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1.6 **Indicate your annual household income from all sources.**

- ☐ $19,999 or less
- ☐ $20,000 to $39,999
- ☐ $40,000 to $49,999
- ☐ $50,000 or more

1.7 **What is your zip code?**

_____

1.8 **What is your telephone area code and prefix?**

___ ___ ____

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The next series of question are about employment.

SECTION 2
EMPLOYMENT

2.1 **What is your primary employment status?** *(Select one only.)*

- ☐ Employed for wages
- ☐ Self-employed
- ☐ Homemaker, no other employment in the last 3 months, *Smokers skip to Section 3; Non-smokers skip to Section 4*
- ☐ Homemaker with other employment within the last 3 months
- ☐ Student, no other employment in the last 3 months, *answer Question 2.2 and then Smokers skip to Section 3; Non-smokers skip to Section 4*
- ☐ Student with other employment within the last 3 months
- ☐ Retired, no other employment in the last 3 months, *Smokers skip to Section 3; Non-smokers skip to Section 4*
- ☐ Retired with other employment within the last 3 months
- ☐ Out-of-work for more than 3 months, *Smokers skip to Section 3; Non-Smokers skip to Section 4*
- ☐ Out-of-work for less than 3 months
- ☐ Unable to work, *Smokers skip to Section 3; Non-smokers skip to Section 4*

If selected "Student, no other employment in last 3 months" in Question 2.1, answer Question 2.2 and then Smokers skip to Section 3, Non-smokers skip to Section 4.

2.2 **Looking at a typical week over the last 3 months, indicate how many hours (to the nearest half-hour) you usually were in school for each day of the week.**

___ hours on Mondays	___ hours on Tuesdays
___ hours on Wednesdays	___ hours on Thursdays
___ hours on Fridays	___ hours on Saturdays
___ hours on Sundays	☐ N/A, not in school in last 3 months

Questions 2.3 through 2.14 will be asked if you have held a job (full or part-time) within the past 3 months.

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2.3 **In the past 3 months, how many jobs (full and part-time) have you held?**

___

Questions 2.4 through 2.14 will be repeated for each job at which you have worked during the last 3 months. For example, if you answered Question 2.3 indicating you have had 3 jobs, you will be asked Questions 2.4 through 2.14 each 3 times. Think of one job at a time with each set of responses.

2.4 **What kind of business or industry is this job in?** *(For example, hospital, newspaper publisher, mail order house, auto repair shop, bank, etc.)*

___

___

___

2.5 **Is this job mainly manufacturing, agriculture, or something else?** *(Select only one.)*

- ☐ Manufacturing
- ☐ Agriculture
- ☐ Other *(Wholesale trade, retail trade, construction, government, etc.)*

2.6 **What kind of work have you been doing in this job during the last 3 months?** *(For example, auto mechanic, bus driver, registered nurse, accountant.)*

___

___

2.7 **During the last 3 months, which days of the week did you normally work at this job?** *(Select all that apply. If you worked a rolling schedule where the days you work vary from week to week, select a typical week.)*

- ☐ Mon
- ☐ Tue
- ☐ Wed
- ☐ Thu
- ☐ Fri
- ☐ Sat
- ☐ Sun

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2.8 **Looking at a typical week over the last 3 months, indicate how many hours (to the nearest half-hour) you usually worked for each day of the week at this job.** *(If you work a rolling schedule, select the same typical week as in Question 2.7. For each day selected in Question 2.7, there should be some hours entered on the corresponding day below. Enter "0" if you do not normally work on a given day.)*

___ hours on Mondays ___ hours on Tuesdays

___ hours on Wednesdays ___ hours on Thursdays

___ hours on Fridays ___ hours on Saturdays

___ hours on Sundays

2.9 **During the last 3 months, have you worked at this job outside of the home or have you worked from your home office the majority of the time?**
☐ Outside of home
☐ From home office

2.10 **In the past 3 months, how many weeks did you actually spend at this job?** *(Think of one month equal to 4 weeks. Include military service and job-related travel. If you have a home office, indicate the number of weeks that you actually spent working in the home office.)*

___ weeks

2.11 **On average for the last 3 months, how many hours did you usually spend at this job each week?** *(If you have a home office, indicate the amount of time that you actually spent in the home office workspace.)*

___ hours

2.12 **At this job has the majority of your day at work been spent indoors or outdoors in the last 3 months?**
☐ indoors
☐ outdoors

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2.13 **Over the past 3 months, have you regularly been exposed to any of the following in this job?**

Engine exhaust ☐ Yes ☐ No
(Such as small or large gas or diesel engines)

Chemicals (*Used by or around you that you can smell or is absorbed into the skin*) ☐ Yes ☐ No, *Smokers skip to Section 3; Non-smokers skip to Section 4*

2.14 **List any chemicals to which you were regularly exposed in this job during the last 3 months.**

Chemical: _____

_____

QUESTIONS 2.4 THROUGH 2.14 WILL BE REPEATED FOR EACH JOB AT WHICH YOU HAVE WORKED DURING THE LAST 3 MONTHS.

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The next series of questions ask about your use of tobacco products.
NON-SMOKERS SKIP THIS SECTION

SECTION 3
SMOKING

3.1 **Do you currently smoke manufactured cigarettes?**
☐ Yes
☐ No

3.2 **In the past 12 months have you smoked manufactured cigarettes on a regular basis? That is, have you smoked at least 1 cigarette per day for the past 12 months?**
☐ Yes
☐ No, *Skip to Section 4*

3.3 **What is the full name of the brand of cigarettes you usually prefer to smoke? (This brand is referred to as "PREFERRED BRAND" below.)** *(Indicate one brand only.)*

_____

3.4 **What is the UPC code from the cigarette pack?**

_____

3.5 **Is that PREFERRED BRAND (from Question 3.3) full flavor, milds, lights, or ultra lights?** *(Select only one.)*
☐ Full Flavor
☐ Milds
☐ Lights
☐ Ultra lights

3.6 **Is that PREFERRED BRAND (from Question 3.3) menthol or non-menthol?** *(Select only one.)*
☐ Menthol
☐ Non-menthol (regular)

3.7 **Is the length of that PREFERRED BRAND (from Question 3.3) king size or shorter, 100s, or 120s?** *(Select only one.)*
☐ King size or shorter
☐ 100s
☐ 120s

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3.8 **Is that PREFERRED BRAND (from Question 3.3) usually soft pack or box?**
(Select only one.)
☐ Soft Pack
☐ Box

3.9 **Is that PREFERRED BRAND (from Question 3.3) filtered or non-filtered?**
(Select only one.)
☐ Filtered
☐ Non-filtered

3.10 **Would you describe yourself as an occasional, moderate, or heavy smoker?**
☐ Occasional
☐ Moderate
☐ Heavy

3.11 **Over the past 3 months, what was the average number of cigarettes you smoked per day?**

_____

3.12 **Over the past 3 months, what was the least number of cigarettes you smoked in a day?**

_____

3.13 **Over the past 3 months what was highest number of cigarettes that you smoked in a day?**

_____

3.14 **In a typical week during the last 3 months, about how many cigarettes did you smoke per day for each day of the week?**

Sun	Mon	Tue	Wed	Thu	Fri	Sat

3.15 **How long have you been smoking this PREFERRED BRAND (from Question 3.3)? *(Provide best estimate.)***
☐ Less than 3 months, *Skip to Section 4*
☐ 3 months to 1 year
☐ More than 1 year

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3.16 **Do you ever buy other brands than your PREFERRED BRAND (from Question 3.3)?**
- ☐ Yes
- ☐ No, *Skip to Question 3.25*

3.17 **What is the full name of the most frequent alternate brand of cigarettes you sometimes smoke? (Referred to as "ALTERNATE BRAND" for the following questions.)** *(Indicate one brand only.)*

_____

3.18 **Is that ALTERNATE BRAND (from Question 3.17) full flavor, milds, lights, or ultra lights?** *(Select only one.)*
- ☐ Full Flavor
- ☐ Milds
- ☐ Lights
- ☐ Ultra lights

3.19 **Is that ALTERNATE BRAND (from Question 3.17) menthol or non-menthol?** *(Select only one.)*
- ☐ Menthol
- ☐ Non-menthol (regular)

3.20 **Is the length of that ALTERNATE BRAND (from Question 3.17) king size or shorter, 100s, or 120s?** *(Select only one.)*
- ☐ King size or shorter
- ☐ 100s
- ☐ 120s

3.21 **Is that ALTERNATE BRAND (from Question 3.17) usually soft pack or box?** *(Select only one.)*
- ☐ Soft pack
- ☐ Box

3.22 **Is that ALTERNATE BRAND (from Question 3.17) filtered or non-filtered?** *(Select only one.)*
- ☐ Filtered
- ☐ Non-filtered

3.23 **What percent of the time did you smoke that ALTERNATE BRAND (from Question 3.17) in the last month?**

_____ %

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3.24 **What percent of the time did you smoke that ALTERNATE BRAND (from Question 3.17) in the last 3 months?**

_____%

3.25 **Have you ever regularly smoked a brand other than your PREFERRED BRAND (from Question 3.3)?**
☐ Yes
☐ No, *Skip to Question 3.33*

3.26 **How many months ago did you switch to your PREFERRED BRAND (from Question 3.3)?**

____ months ago, *if greater than 12 months, skip to Question 3.33*

3.27 **What is the full name of the brand you previously smoked (referred to as "PREVIOUS BRAND" below)?** *(If more than one brand, indicate the brand smoked most often. Indicate one brand only.)*

_____

3.28 **Was that PREVIOUS BRAND (from Question 3.27) full flavor, milds, lights, or ultra lights?** *(Select only one.)*
☐ Full Flavor
☐ Milds
☐ Lights
☐ Ultra lights

3.29 **Was that PREVIOUS BRAND (from Question 3.27) menthol or non-menthol?** *(Select only one.)*
☐ Menthol
☐ Non-menthol (regular)

3.30 **Was the length of that PREVIOUS BRAND (from Question 3.27) king size or shorter, 100s, or 120s?** *(Select only one.)*
☐ King size or shorter
☐ 100s
☐ 120s

3.31 **Was that PREVIOUS BRAND (from Question 3.27) usually soft pack or box?** *(Select only one.)*
☐ Soft pack
☐ Box

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3.32 **Was that PREVIOUS BRAND (from Question 3.27) filtered or non-filtered?**
(Select only one.)
☐ Filtered
☐ Non-filtered

3.33 **Over the past 3 months, how often have you removed the filter on your cigarette before smoking it?**
☐ Always
☐ Sometimes
☐ Rarely
☐ Never

3.34 **Do you often have cigarettes burn up in the ashtray?**
☐ Yes
☐ No, *Skip to Question 3.36*

3.35 **When your cigarette burns up in the ashtray, is that usually after smoking most, some, or very little of the cigarette?**
☐ Most
☐ Some
☐ Very little

3.36 **About how far down do you typically smoke the cigarette before putting it out?**
☐ Almost to the filter
☐ About ¾ of the cigarette
☐ About ½ of the cigarette
☐ About ¼ of the cigarette

3.37 **Do you normally inhale?**
☐ Yes
☐ No, *Skip to Question 3.39*

3.38 **How deeply do you normally inhale?**
☐ Into the mouth and throat
☐ Into the chest and lungs

3.39 **How soon after you wake up do you normally smoke your first cigarette?**
☐ Within 5 minutes
☐ 6 to 30 minutes
☐ More than 30 minutes

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3.40 **Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in movies, etc.?**
- ☐ Yes
- ☐ No

3.41 **Which cigarette would you hate most to give up?**
- ☐ The first one upon awaking
- ☐ All others

3.42 **How many cigarettes per day do you typically smoke?**
- ☐ 10 or less
- ☐ 11 to 20
- ☐ 21 to 30
- ☐ 31 or more

3.43 **Do you smoke more frequently during the first hours after waking than during the rest of the day?**
- ☐ Yes
- ☐ No

3.44 **Do you smoke if you are so ill that you are in bed most of the day?**
- ☐ Yes
- ☐ No

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This next section contains a series of questions that ask about your exposure to the tobacco smoke of others who smoke in your presence. By exposure we mean that you can see or smell the tobacco smoke of others or see others in your presence smoking tobacco products.

SECTION 4
EXPOSURE TO TOBACCO SMOKE OF OTHERS

Questions 4.1 through 4.6 are related to your exposure to tobacco smoke in your WORK ENVIRONMENT during the last 3 months.

4.1 **Within the last 3 months, did you ever work indoors or in an enclosed space at a job where you were regularly exposed to the tobacco smoke of other smokers?**
☐ Yes
☐ No, *Skip to Question 4.7*

4.2 **Over the past 3 months, how many jobs have you held in which you were exposed to the tobacco smoke of other smokers indoors or in an enclosed space on a regular basis?**

_____

You will be asked to answer Questions 4.3 through 4.6 for each of the jobs indicated in Question 4.2. If more than one job is indicated in Question 4.2, think of one job at a time for responses to the series of questions.

4.3 **In this job, within the last 3 months, during which weeks were you regularly exposed to the tobacco smoke of others indoors or in an enclosed space? Think of the last 3 months as 12 weeks, with Week 1 as the first week (3 months ago) and Week 12 as last week.** *(Select all that apply.)*

☐ Week 1 ☐ Week 2 ☐ Week 3 ☐ Week 4 ☐ Week 5 ☐ Week 6

☐ Week 7 ☐ Week 8 ☐ Week 9 ☐ Week 10 ☐ Week 11 ☐ Week 12

4.4 **During the last 3 months, how many days per week on average were you exposed to tobacco smoke from others indoors or in an enclosed space at this workplace?**

____ days per week

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4.5 **During the last 3 months, for how long each day on average were you regularly exposed to tobacco smoke at this workplace indoors or in an enclosed space, including the time spent at the cafeteria and during breaks?**

____ hours per day (to nearest half-hour)

4.6 **Would you say that the amount of tobacco smoke to which you were regularly exposed in this workplace indoors or in an enclosed space was usually light, moderate, or heavy in last 3 months?**

☐ Light
☐ Moderate
☐ Heavy

QUESTIONS 4.3 THROUGH 4.6 WILL BE REPEATED FOR EACH JOB INDICATED IN QUESTION 4.2.

The next series of questions (Questions 4.7 through 4.28) are about your HOME ENVIRONMENT and your exposure to the tobacco smoke of others in your home during the past 3 months.

4.7 **In the past 3 months have you lived with someone in a marital-type relationship?**

☐ Yes
☐ No, *Skip to Question 4.19*

4.8 **At home, did your spouse/partner smoke in your presence during the past 3 months?**

☐ Yes
☐ No, *Skip to Question 4.19*

Questions 4.9 through 4.18 are related to your exposure to the tobacco smoke of your spouse/partner.

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4.9 **What did your spouse/partner smoke in your presence at home in the last 3 months?** *(Select only one.)*

- ☐ Manufactured Cigarettes
- ☐ Cigars
- ☐ Cigarillos
- ☐ Pipes
- ☐ Other product or combination (more than one product), *specify:* _____
  (For example, Roll-your-own cigarettes or bidis or combinations such as cigars plus pipes.)

In this next series of questions (Questions 4.10 through 4.15), you will be asked to differentiate your exposure to tobacco smoke on your workdays versus your NON-workdays.

4.10 **Thinking of your typical workdays during the last 3 months, how often did *your spouse/partner* smoke *PRODUCT* (from Question 4.9) at home when you were together?**

- ☐ 7 workdays per week
- ☐ 5 to 6 workdays per week
- ☐ 2 to 4 workdays per week
- ☐ Rarely
- ☐ Never, *Skip to Question 4.13*
- ☐ No workdays in the past 3 months, *Skip to Question 4.13*

4.11 **On your typical workday in the last 3 months, on average how many PRODUCT (from Question 4.9) did your spouse/partner smoke at home when you were together?**

_____ per workday

4.12 **During the last 3 months, for how long each workday on average were you exposed to your spouse/partner's tobacco smoke from PRODUCT (from Question 4.9) at home when you were together?**

____ hours per workday to the nearest half-hour

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4.13 **Now, thinking of your typical NON-workdays during the last 3 months, how often did your spouse/partner smoke PRODUCT (from Question 4.9) at home when you were together?**

- ☐ 7 NON-workdays per week
- ☐ 5 to 6 NON-workdays per week
- ☐ 2 to 4 NON-workdays per week
- ☐ Rarely
- ☐ Never, *Skip to Question 4.16*
- ☐ No NON-workdays in the past 3 months, *Skip to Question 4.16*

4.14 ***On your typical NON-workday in the last 3 months, on average how many* PRODUCT (from Question 4.9) did your spouse/partner smoke at home when you were together?**

_____ per NON-workday

4.15 **During the last 3 months, for how long each NON-workday on average were you exposed to your spouse/partner's tobacco smoke from PRODUCT (from Question 4.9) at home when you were together?**

____ hours per NON-workday to the nearest half-hour

4.16 **Over the past 3 months, have there been changes in the amount your spouse/partner smoked PRODUCT (from Question 4.9) in your presence at home when you were together?** *(For example, was your spouse/partner away from home for an extended period of time?)*

- ☐ Yes
- ☐ No, *Skip to Question 4.19*

4.17 **During which weeks did the change occur? Think of the last 3 months as 12 weeks, with Week 1 as the first week (3 months ago) and Week 12 as last week.** *(Select all that apply.)*

☐ Week 1 ☐ Week 2 ☐ Week 3 ☐ Week 4 ☐ Week 5 ☐ Week 6

☐ Week 7 ☐ Week 8 ☐ Week 9 ☐ Week 10 ☐ Week 11 ☐ Week 12

4.18 **What kind of change occurred?**

_____

This next series of questions (Questions 4.19 through 4.28) are asked about persons other than your spouse/partner who live in your home or who visit on a regular basis.

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4.19 **Within the last 3 months, were you exposed to tobacco smoke in your home from persons, not including your spouse/partner, who lived in the same residence or who visited regularly?**

☐ Yes
☐ No, *Skip to Question 4.29*

4.20 **How many different people, not including a spouse/partner, exposed you to tobacco smoke in your home during the last 3 months?**

____

You will be asked to answer Questions 4.21 through 4.28 for each person indicated in Question 4.20. If more than one person is indicated in Question 4.20, think of one person at a time for responses to the series of questions.

4.21 **Within the last 3 months, during which weeks were you regularly exposed to the tobacco smoke of this person at your home? Think of the last 3 months as 12 weeks, with Week 1 as the first week (3 months ago) and Week 12 as last week.** ***(Select all that apply.)***

☐ Week 1 ☐ Week 2 ☐ Week 3 ☐ Week 4 ☐ Week 5 ☐ Week 6

☐ Week 7 ☐ Week 8 ☐ Week 9 ☐ Week 10 ☐ Week 11 ☐ Week 12

4.22 **What did this person smoke in your presence in your home in the last 3 months?** ***(Select only one.)***

☐ Manufactured Cigarettes
☐ Cigars
☐ Cigarillos
☐ Pipes
☐ Other product or combination (more than one product), *specify:* _____
(For example, Roll-your-own cigarettes or bidis or combinations such as cigars plus pipes.)

In this next series of questions (Questions 4.23 through 4.28), you will be asked to differentiate your exposure to tobacco smoke from this person on your workdays versus your NON-workdays.

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4.23 **Thinking of your typical workdays in the last 3 months, how often did this person smoke PRODUCT (from Question 4.22) in your home when you were together?**

- ☐ 7 workdays per week
- ☐ 5 to 6 workdays per week
- ☐ 2 to 4 workdays per week
- ☐ Rarely
- ☐ Never, *Skip to Question 4.26*
- ☐ No workdays in the past 3 months, *Skip to Question 4.26*

4.24 **On your typical workday during the last 3 months, on average how many PRODUCT (from Question 4.22) did this person smoke in your home when you were together?**

_____ per workday

4.25 **During the last 3 months, for how long each workday on average were you exposed to this person's tobacco smoke from PRODUCT (from Question 4.22) in your home when you were together?**

_____ hours per workday to the nearest half-hour

4.26 **Now, thinking of your typical NON-workdays, how often during the last 3 months did this person smoke PRODUCT (from Question 4.22) in your home when you were together?**

- ☐ 7 NON-workdays per week
- ☐ 5 to 6 NON-workdays per week
- ☐ 2 to 4 NON-workdays per week
- ☐ Rarely
- ☐ Never, *Skip to Question 4.29*
- ☐ No NON-workdays in the past 3 months, *Skip to Question 4.29*

4.27 **On your typical NON-workday in the last 3 months, on average how many PRODUCT (from Question 4.22) did this person smoke in your home when you were together?**

_____ per NON-workday

4.28 **During the last 3 months, how long each NON-workday on average were you exposed to this person's tobacco smoke from PRODUCT (from Question 4.22) in your home when you were together?**

_____ hours per NON-workday to the nearest half-hour

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QUESTIONS 4.21 THROUGH 4.28 WILL BE REPEATED FOR EACH PERSON INDICATED IN QUESTION 4.20.

This next series of questions (Questions 4.29 through 4.34) ask about your exposure to tobacco smoke while traveling in vehicles (VEHICLE EXPOSURE).

4.29 **Within the last 3 months, have you regularly traveled (daily or at least a couple of times per week) in an enclosed vehicle that was smoky or where you could at least smell the tobacco smoke of others most of the time?**
- ☐ Yes
- ☐ No, *Skip to Question 4.35*

4.30 **How many different vehicles did you regularly travel in during the last 3 months which were smoky or where you could at least smell the tobacco smoke of others most of the time?**

_____

You will be asked to answer Questions 4.31 through 4.34 for each vehicle indicated in Question 4.30. If more than one vehicle is indicated in Question 4.30, think of one vehicle at a time for responses to the series of questions.

4.31 **What type of vehicle was this?** *(Select one for each time this question is repeated for the number of vehicles indicated in Question 4.30.)*
- ☐ Car, truck, or van
- ☐ Train
- ☐ Bus
- ☐ Other, *specify:* _____

4.32 **During the last 3 months, during which weeks were you exposed to the tobacco smoke of others in this VEHICLE (from Question 4.30)? Think of the last 3 months as 12 weeks, with Week 1 as the first week (3 months ago) and Week 12 as last week.** *(Select all that apply.)*

☐ Week 1 ☐ Week 2 ☐ Week 3 ☐ Week 4 ☐ Week 5 ☐ Week 6

☐ Week 7 ☐ Week 8 ☐ Week 9 ☐ Week 10 ☐ Week 11 ☐ Week 12

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Questionnaire

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4.33 **During the last 3 months, approximately how many hours per week were you in this VEHICLE (from Question 4.30) while you were exposed to the tobacco smoke of others?**

_____ hours per week to the nearest half-hour

4.34 **Would you say that the amount of tobacco smoke from others in this VEHICLE (from Question 4.30) was usually light, moderate, or heavy during the last 3 months?**

☐ Light
☐ Moderate
☐ Heavy

QUESTIONS 4.31 THROUGH 4.34 WILL BE REPEATED FOR EACH VEHICLE INDICATED IN QUESTION 4.30.

The next series of questions (Questions 4.35 through 4.40) ask about places where you may have been exposed to tobacco smoke of others other than the places we have already covered (which were your work environment, home environment, vehicle). This would include places such as restaurants, bars, etc. (OTHER LOCATION EXPOSURE)

4.35 **Thinking about just the past 3 months, have you been exposed to the tobacco smoke of others, at least once a week, someplace other than those places that we have already talked about?** *(for example, exposure at least once a week in the same bar or restaurant)*

☐ Yes
☐ No, *Skip to Section 5*

4.36 **In the past 3 months, how many places have you gone where you were exposed to the tobacco smoke of others at least once a week?** *(for example, a bar or a restaurant)*

_____

You will be asked to answer Questions 4.37 through 4.40 for each place indicated in Question 4.36. If more than one place is indicated in Question 4.36, think of one place at a time for responses to the series of questions.

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4.37 **What type of place was it?**

_____

4.38 **During the last 3 months, during which weeks were you exposed to the tobacco smoke of others in the PLACE (from Question 4.37)? Think of the last 3 months as 12 weeks, with Week 1 as the first week (3 months ago) and Week 12 as last week.** *(Select all that apply.)*

☐ Week 1 ☐ Week 2 ☐ Week 3 ☐ Week 4 ☐ Week 5 ☐ Week 6

☐ Week 7 ☐ Week 8 ☐ Week 9 ☐ Week 10 ☐ Week 11 ☐ Week 12

4.39 **In a typical week during the last 3 months, approximately how many hours per week were you in PLACE (from Question 4.37) where you were exposed to the tobacco smoke of others?**

____ hours per week to the nearest half-hour

4.40 **Would you say that the amount of tobacco smoke in the PLACE (from Question 4.37) was usually light, moderate, or heavy during the last 3 months?**

☐ Light
☐ Moderate
☐ Heavy

QUESTIONS 4.37 THROUGH 4.40 WILL BE REPEATED FOR EACH PLACE INDICATED IN QUESTION 4.36.

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Now we are going to talk about various exposures that may occur in your household.

SECTION 5
HOUSEHOLD EXPOSURES

5.1 **How long have you lived at your current address?**
- ☐ Less than 3 months, *Answer Questions 5.2 and 5.3 based on your previous residence*
- ☐ 3 months to less than 1 year
- ☐ 1 to 5 years
- ☐ 6 to 10 years
- ☐ over 10 years

5.2 **How is your home heated?** *(Select all that apply.)*
- ☐ Gas
- ☐ Kerosene
- ☐ Wood
- ☐ Coal
- ☐ Electric
- ☐ Other, *specify:*_____

5.3 **Does your home have an air filtration device in addition to the standard filter usually found on a furnace?**
- ☐ Yes
- ☐ No

5.4 **When you are at home are you exposed on a regular basis to any of the following?**

Engine exhaust ☐ Yes ☐ No
(Such as small or large gas or diesel engines)

Chemicals *(Used by or around you that you can smell or is absorbed into the skin)* ☐ Yes ☐ No, *skip to Section 6*

5.5 **List any chemicals to which you are exposed to at home on a regular basis.** *(Include those used in the home for hobbies or around your home where you smell fumes over an extended period of time.)*

Chemical:_____

_____

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Now we are going to talk about your alcohol use.

SECTION 6
ALCOHOL USE

6.1 **Over the past 3 months, did you drink alcoholic beverages such as beer, wine, or liquor?**
- ☐ Yes
- ☐ No, *Skip to Section 7*

6.2 **Over the past 3 months, how often did you drink beer, wine, or liquor?**
- ☐ Every day
- ☐ 4 to 6 times a week
- ☐ 2 to 3 times a week
- ☐ Once a week
- ☐ 1 to 3 times a month
- ☐ less than once a month

6.3 **Of the beer, wine, or liquor that you consumed over the past 3 months, what percentage of each did you consume?**

Beer: ____ %
Wine ____ %
Liquor ____ %

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Now we are going to ask about your exercise habits.

SECTION 7
PHYSICAL ACTIVITY

7.1 **How often do you usually exercise (at least 10 continuous minutes)?**
- ☐ Daily
- ☐ 3 to 5 times a week
- ☑ 1 to 2 times a week
- ☐ Twice a month
- ☐ Rarely, *Skip to Section 8*
- ☐ Never, *Skip to Section 8*

7.2 **About how long do you exercise each time?**

____ minutes

7.3 **When you exercise for at least 10 minutes, at what level is it?**
- ☐ Light
- ☐ Moderate (*Activities such as brisk walking, bicycling for pleasure, golfing, or dancing*)
- ☐ Vigorous (*Activities such as running, lap swimming, aerobics classes, or fast bicycling*)

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Questionnaire

Protocol No. PM-8450 Covance Study No. 12226-8450

Now we are going to ask about your exercise habits.

SECTION 7
PHYSICAL ACTIVITY

7.1 **How often do you usually exercise (at least 10 continuous minutes)?**
- ☐ Daily
- ☐ 3 to 5 times a week
- ☐ 1 to 2 times a week
- ☐ Twice a month
- ☐ Rarely, *Skip to Section 8*
- ☐ Never, *Skip to Section 8*

7.2 **About how long do you exercise each time?**

_____ minutes

7.3 **When you exercise for at least 10 minutes, at what level is it?**
- ☐ Light
- ☐ Moderate (*Activities such as brisk walking, bicycling for pleasure, golfing, or dancing*)
- ☐ Vigorous (*Activities such as running, lap swimming, aerobics classes, or fast bicycling*)

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Questionnaire

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This section has some general questions about nutrition.

SECTION 8
NUTRITION

8.1 **On average, how many servings per week do you eat or drink the following?**
(Serving size in parentheses.)

Whole milk (8 oz.), dairy products, butter (1 Tbspn), cream (1 Tbspn), ice cream (1/2 cup), etc.	____ servings per week
Red meat (3 oz.), poultry skin (approx. size of breast), organ meat (liver, kidney) (3 oz.)	____ servings per week
Eggs (1 egg), mayonnaise (1 Tbspn)	____ servings per week
Fast food (1 burger), meat taco (1 taco), French fries (1/2 cup)	____ servings per week
Safflower, sunflower, corn, or soybean oils (1 Tbspn)	____ servings per week
Lard, coconut oil, palm oil (1 Tbspn)	____ servings per week

END OF QUESTIONNAIRE

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Interviewer's Instructions

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INTRODUCTORY SECTION

FOR INTERVIEWER ONLY: A few questions have multiple parts requiring a response. In those cases, read each part and get an answer before asking the next part of the questions. For example, in Question A.1 ask, "In the past 12 months, have you smoked manufactured cigarettes?" Wait for an answer and then ask, "In the past 12 months have you smoked cigars?" and etc.

A.1 Select "Yes" for every product you have smoked in the past 12 months, regardless of the frequency the product was smoked and "No" for every product you have not smoked in the past 12 months. (If you have not smoked manufactured cigarettes in the last 12 months, you will skip Section 3, the Smoking Section.) "Bidi" is a form of cigarette found in India; consists of granulated tobacco rolled in a section of Indian ebony leaf and tied with thread. Also called biri or beedi.

A.2 Select "Yes" for every product you have used in the past 12 months, regardless of the frequency the product was used and "No" for every product you have not used in the past 12 months.

A.3 Select "Yes" if you ever regularly smoked manufactured cigarettes. "Regular" in this instance means at least 1 manufactured cigarette per day for at least a year. It does not matter how long ago you smoked them, select "Yes" if you ever smoked at least 1 a day for at least a year.

SECTION 1
DEMOGRAPHICS

1.1

1.2

1.3 **Race**
Select only one answer. If you are of a race not represented, select "Other" and specify the group or groups. If you would like to combine 2 races, select "other" and specify the combination.

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1.4 **Marital Status**
Select only one answer.

1.5 **Degree**
Attending "some college" refers to attendance at an accredited college or university.

1.6 **Household Income**
The household income would include any income from a spouse.

FOR THE INTERVIEWER ONLY: *The subject is allowed the right to refuse to answer this question. If the subject refuses to answer, select "refused" for the response. "Refused" does not show up in the hard copy of the questionnaire and should not be volunteered unless the subject asks or indicates he/she would like to refrain from answering this question.*

1.7 **Zip code**
Provide your 5-digit zip code.

1.8 **Telephone Prefix**
Enter the area code and first 3 numbers of your telephone number.

SECTION 2
EMPLOYMENT

2.1 Select only one answer for your primary employment status. Note that there are 2 listings each for "homemaker," "student," and "retired." If you are a homemaker, student, or retiree that has held a job in the last 3 months, select the appropriate option that includes "with other employment in the last 3 months." We would like to have you answer the questions about employment in this section if you have had a job in the last 3 months. If you are unable to work because of illness/disability, select "unable to work" rather than "out of work."

2.2 **Hours spent in school per each day of the week**
If you have not been a student in the last 3 months, select "N/A." Enter "0" for the days on which you do not typically spend any time in school. Students who

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have not been employed in the last 3 months will skip to Section 3 for Smokers and Section 4 for Non-smokers after this question.

2.3 **Number of jobs**
You are to indicate the number of jobs you have held in the past 3 months. Include full and part-time jobs. If, for example, you had a job for a month, it ended a month ago, and now you have another job, the total would be at least "2" jobs for this question.

2.4 **Kind of business/industry**
You should describe the primary activity at your place of employment. Try to keep your answer concise.

2.5 **Category for job**
If you know your job is not "manufacturing" or "agriculture," select "other."

2.6 **What work do you do?**
Provide your job title or a short description of job responsibilities.

2.7 **Normal workdays per week**
Indicate all the days of the week you typically worked. You should respond for the typical week in the last 3 months, not peak or slow times for your business. If you worked a variable schedule (different days each week), think of a typical "example" week, perhaps the current week's schedule if not a vacation week, and select those days.

2.8 **Usual hours worked per day**
You should respond for the typical week in the last 3 months, not peak or slow times for your business. Enter "0" for the days on which you did not typically work in the last 3 months. If you worked a variable schedule (different days each week), think of a typical "example" week, perhaps the current week's schedule if not a vacation week, and indicate the hours for those days. Generally the days selected in Question 2.7 should contain hours in this question. You must provide one number to the nearest half-hour, not a range for the hours.

2.9 **Job outside home or home office**
If you worked both from a home office and outside the home in the last 3 months,

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select the location where you spent the majority of your time.

2.10 **Weeks in job**
Enter the number of weeks spent at this job in the past 3 months. Include time spent working in a home office. Think of the 3 months totaling 12 weeks in all. If you have worked at this job the entire past 3 months, enter "12."

2.11 **Hours at job**
Enter the average number of hours you worked per week in the last 3 months including any overtime/extra hours. Include time spent working in a home office.

2.12 **Indoor/outdoor**
Think of the majority of your time during the last 3 months only. Did you work at this job indoors or outdoors in that time for a majority of the time.

2.13 **Regular exposure**
Whether something is considered "regular" exposure is up to your interpretation. Select "Yes" for chemicals if you used chemicals or have been around chemicals that you could smell or that could be absorbed into the skin in the last 3 months.

2.14 **List chemicals exposed to**
List all chemicals to which you were regularly exposed in this job in the last 3 months. Be as specific as possible, providing brand names if available.

SECTION 3
SMOKING

3.1

3.2 **Have you smoked 1 per day for 12 months?**
Note that the 1 cigarette per day for 12 months is not an average. Your consumption must include a minimum of 1 cigarette per day for each day during the past 12 months.

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3.3 **Brand name**
You should have a pack of your usual brand of cigarettes with you. Use the pack to provide the exact brand name from the pack.

3.4 **UPC code**
You should have a pack of your usual brand of cigarettes with you. Provide the exact UPC code from the pack.

3.5 **Describe the brand**
Select one. Use the pack as a guide for completing this question.

3.6 **Describe the brand**
Select one. Use the pack as a guide for completing this question.

3.7 **Describe the brand**
Select one. Use the pack as a guide for completing this question. "Regular" length cigarettes are considered "Kings."

3.8 **Describe the brand**
Select one. Use the pack as a guide for completing this question.

3.9 **Describe the brand**
Select one. Use the pack as a guide for completing this question.

3.10 **Describe self**
There is no specific definition for "occasional," "moderate," or "heavy." This question is based on how you would describe yourself as a smoker.

3.11 **Average number per day**
Enter one (whole number) unit, not a range. Give the best approximation of the average number of manufactured cigarettes you smoked per day in the last 3 months.

3.12 **Least number in a day**
Give the best approximation of the least number of manufactured cigarettes you smoked in a day during the last 3 months. Enter a single, whole number, not a

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range.

3.13 **Highest number in a day**
Give the best approximation of the highest number of manufactured cigarettes you smoked in a day during the last 3 months. Enter a single, whole number, not a range.

3.14 **Number per each day**
Enter an average number smoked for each day of a typical week from the last 3 months.

3.15 ***How long smoke this brand***
Provide your best estimate at how long you have been smoking this brand/type.

3.16 **Ever buy other brands?**
Select "Yes" if you sometimes smoke other cigarettes that are a different brand when your usual brand is not available or you are "borrowing" one from someone else.

3.17 **Other brand name**
Provide the most complete name possible for the other brand smoked. If you smoked more than one other brand, use the brand you smoked most frequently. This brand name is inserted into the following questions where "ALTERNATE BRAND" is indicated on your copy of the questionnaire.

3.18 **Describe the alternate brand**
Select one.

3.19 **Describe the alternate brand**
Select one.

3.20 **Describe the alternate brand**
Select one. "Regular" length cigarettes are considered "Kings."

3.21 **Describe the alternate brand**
Select one.

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3.22 **Describe the alternate brand**
Select one.

3.23 **Percent smoke alternate brand**
Provide a number to the nearest percent for the last month. Do not provide a range. Give your best estimate if you are not sure.

3.24 **Percent smoke alternate brand**
Provide a number to the nearest percent for the last 3 months. Do not provide a range. Give your best estimate if you are not sure.

3.25 **Regularly smoke something else**
Was there another brand you regularly smoked before your current "Preferred Brand?"

3.26 **How long ago**
Give the best estimation of the number of months that have passed since switching brands. Provide one number to the nearest whole number, do not give a range.

3.27 **What was the previous brand?**
If you have smoked more than one brand prior to the one you smoke now, give only the other (previous) brand you regularly smoked most often. (For example, if you smoked Brand A for 10 years from 1970 to 1980 and smoked Brand B for 5 years from 1980 to 1985 before switching to your current brand, the "Previous Brand" smoked most often would be "Brand A.") This brand name is inserted into the following questions where "PREVIOUS BRAND" is indicated on your copy of the questionnaire.

3.28 **Describe the previous brand**
Select one.

3.29 **Describe the previous brand**
Select one.

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3.30 **Describe the previous brand**
Select one. "Regular" length cigarettes are considered "Kings."

3.31 **Describe the previous brand**
Select one.

3.32 **Describe the previous brand**
Select one.

3.33 **Removing filter**
This applies only if the entire filter is removed.

3.34 **Cigarettes burn up in ashtray?**
This question refers to your general smoking patterns. Do you smoke the cigarette for a certain amount and then let it burn up in the ashtray or any other place, i.e., the whole cigarette was not smoked by you?

3.35 **How much burn up**
This question refers to your general smoking patterns.

3.36 **How far smoke**
This question refers to your general smoking patterns.

3.37 **Normally inhale**
This question refers to your general smoking patterns.

3.38 **How deeply inhale**
This question refers to your general smoking patterns.

3.39 **How soon smoke**
This question refers to your general smoking patterns.

3.40 **Difficult to refrain**
This question refers to your general smoking patterns.

3.41 **Giving up which one is hardest?**
If given the choice, would you rather give up the first cigarette of the day and

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smoke all the rest of the cigarettes or smoke the first one and give up all the rest of the cigarettes for the day?

3.42 **How many per day**
This question refers to your general smoking patterns.

3.43 **First hours**
This question refers to your general smoking patterns.

3.44 **Smoke if ill**
This question refers to your general smoking patterns.

SECTION 4
EXPOSURE TO THE TOBACCO SMOKE OF OTHERS

4.1 **Smoke exposure at work indoors in last 3 months**
You should answer this question only pertaining to jobs you have held in the last 3 months. If you have been regularly exposed to tobacco smoke at work indoors or in an enclosed space (including during breaks or in the cafeteria), you will be asked to detail the exposure in the following questions. Use your best judgment to determine if your exposure to tobacco smoke at a job is considered "regular" exposure or not. If you have not had exposure to tobacco smoke at work or have worked outdoors only, select "No." If you have not worked in the last 3 months, select "No."

4.2 **How many jobs with exposure?**
This is not the same as the number of jobs you hold. It refers to the number of jobs at which you have had regular exposure to the tobacco smoke of others indoors or in an enclosed space in the last 3 months. If you have been exposed to tobacco smoke indoors or in an enclosed space at more than one job in the past 3 months, this next series of questions will be repeated for each job. Use your best judgment to determine if your exposure to tobacco smoke at a job is considered "regular" exposure or not. You should answer this question only pertaining to the last 3 months.

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4.3 **Weeks exposed at job**
You should answer this question only pertaining to the last 3 months. You will be asked this question for every job at which you have been regularly exposed to the tobacco smoke of others indoors or in an enclosed space in the last 3 months. If the exposure has been continuous through the last 3 months, select all 12 weeks. "Week 1" refers to the beginning of the 3 months and "Week 12" refers to last week. If the exposure was intermittent at the job through the last 3 months, indicate the weeks of the exposure. To help with the timing, think of Week 4 as 2 months ago, Week 8 as 1 month ago, etc. A calendar is available to help with the week numbering.

4.4 **Days per week exposed at job**
You will be asked this question for every job at which you have been regularly exposed to the tobacco smoke of others indoors or in an enclosed space in the last 3 months. Give a single number, not a range.

4.5 **Number of hours per day at job**
You will be asked this question for every job at which you have been regularly exposed to the tobacco smoke of others indoors or in an enclosed space in the last 3 months. Give your best estimate to the nearest half-hour.

4.6 **Amount of smoke in work environment**
You will be asked this question for every job at which you have been regularly exposed to the tobacco smoke of others indoors or in an enclosed space in the last 3 months. There is no specific definition for "light," "moderate," or "heavy" exposure. The amount is determined by your perception of the level of exposure.

4.7 **Have marital type relationship?**
If you have lived with someone as a spouse/partner for the past 3 months or more, select "Yes."

4.8 **Spouse/partner smoke exposure in last 3 months**
You should answer this question only pertaining to the last 3 months. If your spouse/partner has smoked in the last 3 months, but did not smoke in your presence or did not smoke at home, select "No."

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4.9 **Products spouse/partner smokes**

Select the product(s) that your spouse/partner has smoked in your presence at home in the last 3 months. You should answer this question only pertaining to the last 3 months. If your spouse/partner has smoked more than one of these products in your presence at home in the past 3 months, select "other" and specify the products smoked. Also select "other" if your spouse/partner has smoked something other than manufactured cigarettes, cigars, cigarillos, or pipes in your presence at home in the last 3 months and then specify the product smoked. If your spouse/partner has smoked one of the products in the last 3 months, but did not smoke it in your presence or did not smoke it at home, do not include it. "Bidi" is a form of cigarette found in India; consists of granulated tobacco rolled in a section of Indian ebony leaf and tied with thread. Also called biri or beedi.

4.10 **How often on workdays**

This question asks you to determine the exposure on workdays, meaning the days you worked, not the days your spouse/partner worked. When calculating the response to this question, think only of your exposure to your spouse/partner's tobacco smoke at home when you were together on your workdays in the last 3 months. If you have not had a "workday" in the past 3 months, select "No workdays..." Do not select more workdays per week than you actually work.

4.11 **How many on workdays**

This question asks you to determine the exposure on workdays, meaning the days you worked, not the days your spouse/partner worked. When calculating the response to this question, think only of your exposure to your spouse/partner's tobacco smoke at home when you were together on your workdays in the last 3 months. Give your best estimate to a whole number.

4.12 **Hours per workday**

This question asks you to determine the exposure on workdays, meaning the days you worked, not the days your spouse/partner worked. When calculating the response to this question, think only of your exposure to your spouse/partner's tobacco smoke at home when you were together on your workdays in the last 3 months. Give your best estimate to the nearest half-hour per day.

4.13 **How often on NON-workdays**

This question asks you to determine the exposure on NON-workdays, meaning

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the days you didn't work, not the days your spouse/partner didn't work. When calculating the response to this question, think only of your exposure to your spouse/partner's tobacco smoke at home when you were together on your NON-workdays in the last 3 months. If you have not had a "NON-workday" in the past 3 months, select "No NON-workdays..." Do not select more NON-workdays per week than you actually have.

4.14 **How many on NON-workdays**
This question asks you to determine the exposure on NON-workdays, meaning the days you didn't work, not the days your spouse/partner didn't work. When calculating the response to this question, think only of your exposure to your spouse/partner's tobacco smoke at home when you were together on your NON-workdays in the last 3 months. Give your best estimate to a whole number.

4.15 **Hours per NON-workday**
This question asks you to determine the exposure on NON-workdays, meaning the days you didn't work, not the days your spouse/partner didn't work. When calculating the response to this question, think only of your exposure to your spouse/partner's tobacco smoke at home when you were together on your NON-workdays in the last 3 months. Give your best estimate to the nearest half-hour per day.

4.16 **Any change in exposure**
When determining the response to this question, think only of changes to your exposure to your spouse/partner's tobacco smoke at home when you were together in the last 3 months. If, for example, your spouse usually smoked at home in your presence but was away on a business trip for 2 weeks during the last 3 months, select "Yes" for a change.

4.17 **Weeks of change**
When determining the response to this question, think only of changes to your exposure to your spouse/partner's tobacco smoke at home when you were together in the last 3 months. If, for example, your spouse usually smoked at home in your presence but was away on a business trip for 2 weeks during the last 3 months, indicate the 2 weeks of change. "Week 1" refers to the beginning of the 3 months and "Week 12" refers to last week. If the change was intermittent through the last 3 months, indicate the weeks of the change. To help with the

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timing, think of Week 4 as 2 months ago, Week 8 as 1 month ago, etc. A calendar is available to help with the week numbering.

4.18 **Kind of change**
When determining the response to this question, think only of changes to your exposure to *your spouse/partner's tobacco smoke at home when you were* together in the last 3 months. Describe the change that occurred. If, for example, your spouse usually smoked at home in your presence but was away on a business trip for 2 weeks during the last 3 months, indicate "away from home, no exposure during that time."

4.19 **Smoke exposure at home from others in last 3 months**
You should answer this question only pertaining to the last 3 months. If another household member or regular visitor has smoked in the last 3 months, but did not smoke in your presence or did not smoke in your home, select "No."

4.20 **Number of people**
You should answer this question only pertaining to the last 3 months. Calculate the number of household members other than your spouse/partner plus any regular visitors who exposed you to tobacco smoke in your home. If you have been exposed to tobacco smoke of more than one other household member or regular visitor in the past 3 months, this next series of questions will be repeated for each person. Give a single, whole number, not a range.

4.21 **Weeks exposed**
You should answer this question only pertaining to the last 3 months. You will be asked this question for every other household member or regular visitor who smoked in your presence in your home in the last 3 months. If the exposure has been continuous through the last 3 months, select all 12 weeks. "Week 1" refers to the beginning of the 3 months and "Week 12" refers to last week. If the exposure was intermittent through the last 3 months, indicate the weeks of the exposure. To help with the timing, think of Week 4 as 2 months ago, Week 8 as 1 month ago, etc. A calendar is available to help with the week numbering.

4.22 **Products others smoke**
Select the product(s) that another household member or regular visitor has smoked in your presence in your home in the last 3 months. You will be asked

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this question for every other household member or regular visitor who smoked in your presence in your home in the last 3 months. You should answer this question only pertaining to the last 3 months If this other household member or regular visitor has smoked more than one of these products in your presence at your home in the past 3 months, select "other" and specify the products smoked. Also select "other" if this household member or regular visitor has smoked something other than manufactured cigarettes, cigars, cigarillos, or pipes in your presence in your home in the last 3 months and then specify the product smoked. If this household member or regular visitor has smoked one of the products in the last 3 months, but did not smoke it in your presence or did not smoke it in your home, do not include it. "Bidi" is a form of cigarette found in India; consists of granulated tobacco rolled in a section of Indian ebony leaf and tied with thread. Also called biri or beedi.

4.23 **How often on workdays**

You will be asked this question for every other household member or regular visitor who smoked in your presence in your home in the last 3 months. This question asks you to determine the exposure on workdays, meaning the days you worked, not the days this household member or regular visitor worked. When calculating the response to this question, think only of your exposure to this household member or regular visitor's tobacco smoke in your home when you were together on your workdays. If you have not had a "workday" in the past 3 months, select "No workdays..." Do not select more workdays per week than you actually work. You should think of one household member or regular visitor at a time.

4.24 **How many on workdays**

You will be asked this question for every other household member or regular visitor who smoked in your presence in your home in the last 3 months. This question asks you to determine the exposure on workdays, meaning the days you worked, not the days this household member or regular visitor worked. When calculating the response to this question, think only of your exposure to this household member or regular visitor's tobacco smoke in your home when you were together on your workdays. Give your best estimate to a whole number. You should think of one household member or regular visitor at a time.

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4.25 **Hours per workday**
You will be asked this question for every other household member or regular visitor who smoked in your presence in your home in the last 3 months. This question asks you to determine the exposure on workdays, meaning the days you worked, not the days this household member or regular visitor worked. When calculating the response to this question, think only of your exposure to this household member or regular visitor's tobacco smoke in your home when you were together on your workdays. Give your best estimate to the nearest half-hour per day. You should think of one household member or regular visitor at a time.

4.26 **How often on NON-workdays**
You will be asked this question for every other household member or regular visitor who smoked in your presence in your home in the last 3 months. This question asks you to determine the exposure on NON-workdays, meaning the days you didn't work, not the days this household member or regular visitor didn't work. When calculating the response to this question, think only of your exposure to this household member or regular visitor's tobacco smoke in your home when you were together on your NON-workdays. If you have not had a "NON-workday" in the past 3 months, select "No NON-workdays..." Do not select more NON-workdays per week than you actually have. You should think of one household member or regular visitor at a time.

4.27 **How many on NON-workdays**
You will be asked this question for every other household member or regular visitor who smoked in your presence in your home in the last 3 months. This question asks you to determine the exposure on NON-workdays, meaning the days you didn't work, not the days this household member or regular visitor didn't work. When calculating the response to this question, think only of your exposure to this household member or regular visitor's tobacco smoke in your home when you were together on your NON-workdays. Give your best estimate to a whole number. You should think of one household member or regular visitor at a time.

4.28 **Hours per NON-workday**
You will be asked this question for every other household member or regular visitor who smoked in your presence in your home in the last 3 months. This question asks you to determine the exposure on NON-workdays, meaning the

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days you didn't work, not the days this household member or regular visitor didn't work. When calculating the response to this question, think only of your exposure to this household member or regular visitor's tobacco smoke in your home when you were together on your NON-workdays. Give your best estimate to the nearest half-hour per day. You should think of one household member or regular visitor at a time.

4.29 **Smoke exposure in vehicle in last 3 months**
You should answer this question only pertaining to the last 3 months. This question pertains to the tobacco smoke of others in enclosed vehicles only. "Regular" travel is defined as traveling in a smoky vehicle at least a couple times a week.

4.30 **Number of vehicles**
You should answer this question only pertaining to the last 3 months. Include each vehicle in which you were exposed to the tobacco smoke of others (that is, each car should be counted separately). For example, if you were exposed to the tobacco smoke of others in 2 different cars, truck, and a train in the last 3 months, the total would be "4 different vehicles." If you have been exposed to tobacco smoke of others in more than one vehicle in the past 3 months, this next series of questions will be repeated for each vehicle. Give one, single whole number, not a range.

4.31 **Type of vehicle**
You should answer this question only pertaining to the last 3 months. You will be asked this question for every vehicle in which you were exposed to the tobacco smoke of others in the last 3 months. You should think of one vehicle at a time. For example, if you were exposed to the tobacco smoke of others in 2 cars, a truck, and a train in the last 3 months, this question would be repeated four times (in the series) and the types of vehicles would be "car, truck, and van" the for the first 3 repeats of these questions and "train" for the fourth repeat.

4.32 **Which weeks**
You should answer this question only pertaining to the last 3 months. You will be asked this question for every vehicle in which you have been exposed to the tobacco smoke of others in the last 3 months. You should think of one vehicle at a time. If the exposure in this vehicle has been continuous through the last 3

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months, indicate all 12 weeks. "Week 1" refers to the beginning of the 3 months and "Week 12" refers to last week. To help with the timing, think of Week 4 as 2 months ago, Week 8 as 1 month ago, etc. A calendar is available to help with the week numbering.

4.33 **Hours per week**

You should answer this question only pertaining to the last 3 months. You will be asked this question for every vehicle in which you have been exposed to the tobacco smoke of others in the last 3 months. You should think of one vehicle at a time. When calculating the response to this question, think only of your exposure in this vehicle. Give your best estimate to the nearest half-hour per week.

4.34 **Amount in vehicle**

You should answer this question only pertaining to the last 3 months. You will be asked this question for every vehicle in which you have been exposed to the tobacco smoke of others in the last 3 months. You should think of one vehicle at a time. When determining the response to this question, think only of your exposure in this vehicle. There is no specific definition for "light," "moderate," or "heavy" exposure. The amount is determined by your perception of the level of exposure.

4.35 **Smoke exposure in other place in last 3 months**

You should answer this question only pertaining to the last 3 months. This question pertains to places other than your home, work, or vehicles. Only include places in which you were exposed to the tobacco smoke of others at least once a week in the last 3 months. Think of places in which you were regularly exposed to the tobacco smoke of others, meaning at least once a week in the last 3 months. Do not include your own smoke in other places.

4.36 **Number of places**

You should answer this question only pertaining to the last 3 months. Calculate the number of different places in which you were exposed to the tobacco smoke of others at least once per week in the last 3 months. If, for example, you were exposed to tobacco smoke in 2 different bars at least once a week, count each bar separately. If you have been exposed to tobacco smoke of others in more than one place in the past 3 months, this next series of questions will be repeated for *each place. Give one, single whole number, not a range.*

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4.37 **Type of place**

You should answer this question only pertaining to the last 3 months. You will be asked this question for every different place in which you were exposed to tobacco smoke of others at least once per week in the last 3 months. You should think of one place at a time. The name of the specific place is not necessary. Indicate "bar," "restaurant," etc. as appropriate. The same type of place may be repeated for each time this question is repeated for each different specific place, as appropriate. For example, if you were in 2 different bars, you would answer "bar" for the type each time the question was repeated. Be sure to keep the different places clear in your mind as you answer the questions even when the type of place is the same.

4.38 **Which weeks**

You should answer this question only pertaining to the last 3 months. You will be asked this question for every place in which you have been exposed to the tobacco smoke of others in the last 3 months. You should think of one place at a time. If the exposure has been continuous through the last 3 months, indicate all 12 weeks. "Week 1" refers to the beginning of the 3 months and "Week 12" refers to last week. To help with the timing, think of Week 4 as 2 months ago, Week 8 as 1 month ago, etc. A calendar is available to help with the week numbering.

4.39 **Hours per week**

You should answer this question only pertaining to the last 3 months. You will be asked this question for every place in which you have been exposed to tobacco smoke of others at least once per week in the last 3 months. You should think of one place at a time. When calculating the response to this question, think only of your exposure in this place. Give your best estimate to the nearest half-hour per week.

4.40 **Amount in place**

You should answer this question only pertaining to the last 3 months. You will be asked this question for every place in which you have been exposed to tobacco smoke of others at least once per week in the last 3 months. You should think of one place at a time. When determining the response to this question, think only of your exposure in this place. There is no specific definition for "light," "moderate," or "heavy" exposure. The amount is determined by your perception

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of the level of exposure.

SECTION 5
HOUSEHOLD EXPOSURES

5.1 **How long live in current home?**
If you have lived in your current home for less than 3 months, use your previous residence for your responses to Questions 5.2 and 5.3.

5.2 **How heat home?**
If you have lived in your current home for less than 3 months, use your previous residence for your response to this question. Select multiple answers if you heat your home with more than one method. If you burn a fire in a fireplace for decorative purposes, it does not count as a heating method.

5.3 **Filtration**
If you have lived in your current home for less than 3 months, use your previous residence for your response to this question. An air filtration device can include a portable unit if you use it regularly. This does not include the standard furnace filter usually found in a furnace.

5.4 **Exposed to these at home?**
Chemicals can include cleaning products, hair dye, perms, nail polish remover, etc. if the exposure is "regular." What is considered "regular" exposure will be up to your interpretation.

5.5 **List chemicals, etc.**
Please be as specific as possible, giving the brand name of any products if possible. What is considered "regular" exposure will be up to your interpretation.

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SECTION 6
ALCOHOL USE

6.1 **Drink alcohol?**
This question pertains to the last 3 months only.

6.2 **How often**
This question pertains to the last 3 months only. Count every day on which you had at least 1 serving of beer, wine, or liquor..

6.3 **Percentage of each**
Thinking of the beer, wine, and liquor that you drank over the past 3 months as totaling 100%, what percentage would you give to each that you consume. If, for example, you did not drink beer, but drank wine and liquor each about half the time, your answer would be "Beer: 0%, Wine: 50%, Liquor: 50%." Round the percentages to no decimal places. It is possible that your total might not be 100% if, for example, you smoked each for a third of the time, you would list "33%" for each, totaling 99%.

SECTION 7
PHYSICAL ACTIVITY

7.1 **How often exercise?**
Define "Exercise" as for at least 10 continuous minutes that at least causes a slight sweating or slight increase in breathing or heart rate.

7.2 **How long**
Give a single unit of time, not a range.

7.3 **Level**
Using the examples provided, choose the best one.

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SECTION 8
NUTRITION

8.1 **How many servings eat?**
Listen carefully to the categories when analyzing how many servings you eat per week of each of the items. Specifically, the first group is asking about whole milk and whole milk products, real butter, real cheese (not processed), not the "lite" or "skim" products. A "serving" refers to the amount of an item indicated in parentheses and listed as a serving on the product label. This will vary from item to item (e.g., 1 Tablespoon of mayonnaise and 8 ounces of whole milk would both be considered a "serving"). Even if you eat more than one serving in a single sitting, count each serving separately. Total the number of servings you have eaten in each category for the different items combined together. For example, if you typically eat 3 eggs and 2 sandwiches with a serving of mayonnaise on them per week, the "eggs, mayonnaise" category would have "5 servings per week" as the total.

END OF QUESTIONNAIRE

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Weekly Survey Guidelines

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WEEKLY SURVEY
For each Bio-Sample Collection Visit

Instructions for the Interviewer to clarify specific questions on the Weekly Survey

The Interviewer is not to deviate from the clarifications given in this document or on the computer "help" button for individual questions. If the subject is confused about how to answer a question, you can refer to these guidelines for that particular question, but do not provide your personal interpretation of the question. Some of the questions are intentionally vague to allow for the subject's personal interpretation and perception. If there are no guidelines given for a particular question, you can repeat the question slowly to encourage the subject's response. These guides are not to be shown to the subject, but to serve as clarification for the Interviewer.

A hard copy of the survey will be given to the subject to follow along with during the interview. A hard copy of the survey will also be available to you, the Interviewer, along with these guidelines. Your copy of the survey will include "skip to" references that will be removed from the subject's copy. Some questions may be skipped based on the subject's response to a previous question. For example, if the subject is not employed, he/she will not be asked the additional questions pertaining to his/her employment. The subject should not see the computer screen or your version of the hard copy of the survey.

For questions requiring a numerical response, the computer will not allow you to enter a range. You must enter a specific number. The only questions allowing a range will be those where each range is given as a specific possible checkbox. If the subject provides a range, ask him/her to give one number, the subject's best estimate. Questions that ask for a number of hours should be given to the nearest half-hour.

At the beginning of the survey you will ask the subject whether he/she smokes or uses certain items. The computer will automatically skip the questions/sections that are not applicable to the non-smoker. The computer will also automatically skip other non-applicable questions based on subject's answers to related questions (i.e., if the subject has never smoked a different brand, he/she will not be asked to describe the other brand he/she smoked). The hard copy of the survey will contain all the questions, whether to be skipped or not, and you may have to guide the subject to the next applicable question (use page numbers and question numbers to guide the subject).

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Sections and some groups of questions are prefaced with introductory comments/clarifications. Be sure to read these aloud to the subject as well. When skipping non-applicable questions, these introductory statements should still be read prior to the question to which you are skipping. For example, if your answer to Question 2.1 prompts you to skip to Question 2.3 and there is an introductory statement appearing before Question 2.3, be sure not to skip the introductory statement that appears before the question when you skip Question 2.2. The computer should automatically take you to the applicable introductory comments.

Some portions of the survey may also be repeated several times depending on an answer to a previous question (for example, questions about employment will be repeated for every job the subject has held in the last 3 months). The computer will automatically repeat the questions as appropriate, but you will need to guide the subject through the repeats on his/her hard copy of the survey. You will also need to keep the subject thinking of the same job/person/vehicle/place through the same series of the repeated questions. The computer questions will assist you with prompts. For example, where "this job" is indicated in the hard copy, the computer may insert "this first job" for the first round, "this second job" for the second series, etc.

Some of the questions contain references to a previous question and the response from the subject in that prior question. In those cases the computer will automatically fill in the subject's response from the indicated question on the computer-generated question. The hard copy will contain a reference to the item in all capital letters and the question number to which it refers. For example, where the survey reads "PREFERRED BRAND" on the hard copy, the computer-generated question will fill in the subject's specific preferred brand as provided as a response to an earlier question. If the subject's preferred brand is "X," the computer-generated question will read "How long have you been smoking X?" instead of "How long have you been smoking PREFERRED BRAND (from Question x.x)?" as the hard copy will read.

The computer will not accept an inappropriate or impossible response. If, for example, the subject states they were exposed to tobacco smoke for 25 hours per day on average, the computer would not accept that response.

The subject is allowed to go back to a question and change his/her response within the interview. Once the interview is over, there will be no changes.

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The survey will be timed by the computer starting after you enter a response to the first question and stopping when you have answered the last question. Once the survey is complete, thank the subject for his/her honest answers, print a hard copy of his/her answers, log off as instructed, and pick up and file the hard copy.

NOTE: Because these guidelines are meant to be read aloud to the subject, they are written in the second person to be addressed to the subject. "You" and "your" refers to the subject. There are a few "FOR INTERVIEWER ONLY" portions in these guidelines that should not be read aloud to the subject. You can read the "helps" for specific questions aloud to the subject, but do not show the subject a hard copy or the computer screen.

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WEEKLY SURVEY

INTRODUCTORY QUESTIONS

A.1 **Since the last time you were interviewed, have you smoked any of the following?** *(Select "Yes" or "No" for each product.)*

Manufactured cigarettes:	☐ Yes	☐ No
Cigars:	☐ Yes	☐ No
Cigarillos:	☐ Yes	☐ No
Pipe:	☐ Yes	☐ No
Other, *specify*: _____	☐ Yes	☐ No

(For example, Roll-your-own cigarettes or bidis.)

A.2 **Since the last time you were interviewed, have you used any of the following nicotine-containing products?** *(Select "Yes" or "No" for each product.)*

Snuff:	☐ Yes	☐ No
Chewing Tobacco:	☐ Yes	☐ No
Nicotine gum or lozenges	☐ Yes	☐ No
Nicotine inhalers:	☐ Yes	☐ No
Nicotine Patches:	☐ Yes	☐ No
Nicotine Sprays:	☐ Yes	☐ No
Other, *specify*: _____	☐ Yes	☐ No

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1 **How did you arrive at this facility?** *(Select the one answer that was your main mode of transportation.)*
- ☐ Car, truck, or van
- ☐ Train
- ☐ Subway
- ☐ Public bus
- ☐ Taxicab
- ☐ Walked the full distance
- ☐ Bike
- ☐ Motorcycle
- ☐ Other, *specify:*_____

2 **What was your primary activity in the last 8 to 10 hours?**
- ☐ Working at your employment
- ☐ Sleeping
- ☐ NON-workday activities
- ☐ Other, *specify:*_____

IF ANSWER "NO" FOR "MANUFACTURED CIGARETTES" IN QUESTION *A.1, SKIP QUESTIONS 3 THROUGH 15.*

3 **In the past 3 days, have you smoked manufactured cigarettes on a regular basis? That is, have you smoked at least 1 cigarette per day?**
- ☐ Yes
- ☐ No, *Skip to Question 16*

4 **Within the past 3 days, on average, how many cigarettes did you smoke per day?**

_____

5 **For the most part, did you smoke your usual brand of cigarettes (your PREFERRED BRAND)?**
- ☐ Yes
- ☐ No, brand name and type:_____

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6 **Indicate any changes in the way that you smoked since your last interview.** *(Select all that apply.)*
- ☐ Changed brands
- ☐ Switched to lower tar product, *specify product (brand name)*_____
- ☐ Switched to higher tar product, *specify product (brand name)*_____
- ☐ Started using another tobacco or nicotine product in addition to cigarettes
- ☐ Reduced the number of cigarettes smoked
- ☐ Increased the number of cigarettes smoked
- ☐ Stopped smoking cigarettes
- ☐ No change *(cannot select this option if any other boxes are selected)*

7 **In the past 3 days did you smoke other brands than your PREFERRED BRAND?**
- ☐ Yes
- ☐ No, *Skip to Question 16*

8 **How many different brands did you smoke other than your PREFERRED BRAND in the last 3 days?**

____

You will be asked to answer Questions 9 through 15 for each of the brands indicated in Question 8. If more than one brand is indicated in Question 8, think of one brand at a time for responses to the series of questions.

9 **What is the full name this alternate brand of cigarettes you smoked in the last 3 days? (Referred to as "ALTERNATE BRAND" for the following questions.)** *(Indicate one brand only.)*

_____

10 **Is this ALTERNATE BRAND (from Question 9) full flavor, milds, lights, or ultra lights?** *(Select one only.)*
- ☐ Full Flavor
- ☐ Milds
- ☐ Lights
- ☐ Ultra lights

11 **Is this ALTERNATE BRAND (from Question 9) menthol or non-menthol?** *(Select one only.)*
- ☐ Menthol
- ☐ Non-menthol (regular)

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12 **Is the length of this ALTERNATE BRAND (from Question 9) king size or shorter, 100s, or 120s?** *(Select one only.)*
- ☐ King size or shorter
- ☐ 100s
- ☐ 120s

13 **Is this ALTERNATE BRAND (from Question 9) usually soft pack or box?** *(Select one only.)*
- ☐ Soft pack
- ☐ Box

14 **Is this ALTERNATE BRAND (from Question 9) filtered or non-filtered?** *(Select one only.)*
- ☐ Filtered
- ☐ Non-filtered

15 **How many of the ALTERNATE BRAND (from Question 9) did you smoke in the last 3 days?**

____

QUESTIONS 9 THROUGH 15 WILL BE REPEATED FOR EACH BRAND INDICATED IN QUESTION 8.

Questions 16 through 20 are related to your exposure to tobacco smoke in your WORK ENVIRONMENT during the last 3 days.

16 **Within the last 3 days, did you work indoors or in an enclosed space where you were exposed to tobacco smoke of others?**
- ☐ Yes
- ☐ No, *Skip to Question 21*

17 **Over the past 3 days, how many jobs have you worked at in which you were exposed to the tobacco smoke of other smokers indoors or in an enclosed space on a regular basis?**

____

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You will be asked to answer Questions 18 through 20 for each of the jobs indicated in Question 17. If more than one job is indicated in Question 17, think of one job at a time for responses to the series of questions.

18 **During which of the last 3 days were you exposed to tobacco smoke from others at this workplace indoors or in an enclosed space? (Think of Day 1 as the beginning of the 3 days and Day 3 as yesterday.)** *(Select all that apply.)*

☐ Day 1 ☐ Day 2 ☐ Day 3

19 **For how long each day on average during the last 3 days were you regularly exposed to tobacco smoke at this workplace indoors or in an enclosed space, including the time spent at the cafeteria and during breaks?**

____ hours per day to the nearest half-hour

20 **Would you say that the amount of tobacco smoke to which you were exposed in this workplace indoors or in an enclosed space was usually light, moderate, or heavy in the last 3 days?**

☐ Light
☐ Moderate
☐ Heavy

QUESTIONS 18 THROUGH 20 WILL BE REPEATED FOR EACH JOB INDICATED IN QUESTION 17.

The next series of questions (Questions 21 through 36) are about your HOME ENVIRONMENT and your exposure to the tobacco smoke of others in your home during the past 5 days.

21 **Do you live with someone in a marital type relationship?**

☐ Yes
☐ No, *Skip to Question 30*

22 **At home, did your spouse/partner smoke in your presence during the past 3 days?**

☐ Yes
☐ No, *Skip to Question 30*

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Questions 23 through 29 are related to your exposure to the tobacco smoke of your spouse/partner.

23 **What did your spouse/partner smoke in your presence in the last 3 days?** *(Select only one.)*
- ☐ Manufactured Cigarettes
- ☐ Cigars
- ☐ Cigarillos
- ☐ Pipes
- ☐ Other product or combination (more than one product), *specify:* _____ *(For example, Roll-your-own cigarettes or bidis or combinations such as cigars plus pipes.)*

24 **During the last 3 days, how often did your spouse/partner smoke PRODUCT (from Question 23) at home when you were together?**
- ☐ Every day (all 3 days)
- ☐ 2 days
- ☐ 1 day
- ☐ Never, *Skip to Question 30*

25 **In the last 3 days, on average how many PRODUCT (from Question 23) did your spouse/partner smoke per day at home when you were together?**

_____ per day

26 **During the last 3 days, for how long each day on average were you exposed to your spouse/partner's tobacco smoke from PRODUCT (from Question 23) at home when you were together?**

____ hours per day to the nearest half-hour

27 **Over the past 3 days, have there been any changes in the amount your spouse/partner smoked PRODUCT (from Question 23) in your presence at home when you were together?** *(For example, was your spouse/partner away from home?)*
- ☐ Yes
- ☐ No, *Skip to Question 30*

28 **During which of the last 3 days did the change occur? (Think of Day 1 as the beginning of the 3 days and Day 3 as yesterday.)** *(Select all that apply.)*

☐ Day 1 ☐ Day 2 ☐ Day 3

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29 **What kind of change occurred?**

_____

This next series of questions (Questions 30 through 36) are asked about persons other than your spouse/partner who live in your home or who visit on a regular basis.

30 **Within the last 3 days, were you exposed to tobacco smoke from persons other than a spouse/partner who lived in the same residence or who visited regularly?**
☐ Yes
☐ No, *Skip to Question 37*

31 **How many different people, not including a spouse/partner, exposed you to tobacco smoke in your home during the last 3 days?**

____

You will be asked to answer Questions 32 through 36 for each person indicated in Question 31. If more than one person is indicated in Question 31, think of one person at a time for responses to the series of questions.

32 **On which of the last 3 days were you exposed to the tobacco smoke of this person at your home? Think of Day 1 as the beginning of the 3 days and Day 3 as yesterday.** *(Select all that apply.)*

☐ Day 1 ☐ Day 2 ☐ Day 3

33 **What did this person smoke in your presence in the last 3 days?** *(Select only one.)*
☐ Manufactured Cigarettes
☐ Cigars
☐ Cigarillos
☐ Pipes
☐ Other product or combination (more than one product), *specify:* _____
(For example, Roll-your-own cigarettes or bidis or combinations such as cigars plus pipes.)

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34 **In the last 3 days, how often did this person smoke PRODUCT (from Question 33) in your home when you were together?**
- ☐ Every day (all 3 days)
- ☐ 2 days
- ☐ 1 day
- ☐ Never, *Skip to Question 37*

35 **On a typical day during the last 3 days, on average how many PRODUCT (from Question 33) did this person smoke in your home when you were together?**

_____ per day

36 **During the last 3 days, for how long each day on average were you exposed to this person's tobacco smoke from PRODUCT (from Question 33) at your home when you were together?**

_____ hours per day to the nearest half-hour

QUESTIONS 32 THROUGH 36 WILL BE REPEATED FOR EACH PERSON INDICATED IN QUESTION 31.

This next series of questions (Questions 37 through 42) ask about your exposure to tobacco smoke while traveling in vehicles (VEHICLE EXPOSURE).

37 **Within the last 3 days, have you traveled in an enclosed vehicle that was smoky or where you could at least smell tobacco smoke of others most of the time?**
- ☐ Yes
- ☐ No, *Skip to Question 43*

38 **How many different vehicles did you travel in during the last 3 days which were smoky or where you could at least smell tobacco smoke of others most of the time?**

_____

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Protocol No. PM-8450 Covance Study No. 12226-8450

You will be asked to answer Questions 39 through 42 for each vehicle indicated in Question 38. If more than one vehicle is indicated in Question 38, think of one vehicle at a time for responses to the series of questions.

39 **What type of vehicle was this?** *(Select one for each time this question is repeated for the number of vehicles indicated in Question 38.)*
- ☐ Car, truck, or van
- ☐ Train
- ☐ Bus
- ☐ Other, *specify:* _____

40 **On which of the last 3 days were you exposed to the tobacco smoke in this VEHICLE (from Question 39)? Think of Day 1 as the beginning of the 3 days and Day 3 as yesterday.** *(Select all that apply.)*

☐ Day 1 ☐ Day 2 ☐ Day 3

41 **In the last 3 days, approximately how many hours were you in this VEHICLE (from Question 39) while you were exposed to the tobacco smoke of others?**

_____ hours to the nearest half-hour

42 **Would you say that the amount of tobacco smoke from others in this VEHICLE (from Question 39) was usually light, moderate, or heavy during the last 3 days?**
- ☐ Light
- ☐ Moderate
- ☐ Heavy

QUESTIONS 39 THROUGH 42 WILL BE REPEATED FOR EACH VEHICLE INDICATED IN QUESTION 38.

The next series of questions (Questions 43 through 48) ask about places where you may have been exposed to tobacco smoke of others, not including places we have already covered (which were your work environment, home environment, vehicle). This would include places such as restaurants, bars, etc. (OTHER LOCATION EXPOSURE)

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43 **Thinking about just the past 3 days, have you been exposed to the tobacco smoke of others, someplace other than those places that we have already talked about?** *(e.g., a bar or a restaurant)*
☐ Yes
☐ No, *Skip to Survey End*

44 **In the past 3 days, how many places have you gone where you were exposed to the tobacco smoke of others?** *(e.g., in a bar or a restaurant)*

_____

You will be asked to answer Questions 45 through 48 for each place indicated in Question 44. If more than one place is indicated in Question 44, think of one place at a time for responses to the series of questions.

45 **What type of place was it?**

_____

46 **On which of the last 3 days were you exposed to the tobacco smoke of others in this PLACE (from Question 45)? Think of Day 1 as the beginning of the 3 days and Day 3 as yesterday.** *(Select all that apply.)*

☐ Day 1 ☐ Day 2 ☐ Day 3

47 **During the last 3 days, approximately how many hours were you in PLACE (from Question 45) where you were exposed to the tobacco smoke of others?**

____ hours to the nearest half-hour

48 **Would you say that the amount of tobacco smoke in the PLACE (from Question 45) was usually light, moderate, or heavy during the last 3 days?**
☐ Light
☐ Moderate
☐ Heavy

QUESTIONS 45 THROUGH 48 WILL BE REPEATED FOR EACH PLACE INDICATED IN QUESTION 44.

END INTERVIEW

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APPENDIX E – Interviewer Instructions, Questionnaire, and Weekly Surveys

Weekly Survey Guidelines

Protocol No. PM-8450 Covance Study No. 12226-8450

INTRODUCTORY SECTION

A.1 Select "Yes" for every product you have smoked since the last interview, regardless of the frequency the product was smoked. Select "No" for each product you have not smoked since the last interview. If you have not smoked manufactured cigarettes since you were last interviewed, you will skip Questions 3 through 14, the Smoking questions. "Bidi" is a form of cigarette found in India; consists of granulated tobacco rolled in a section of Indian ebony leaf and tied with thread. Also called biri or beedi.

A.2 Select "Yes" for every product you have used since your last interview, regardless of how frequently the product was used. Select "No" for every product you have not used since your last interview.

1. **Transportation**
Select the main mode of transportation.

2. **Primary activity**
If this is a morning visit and you were mainly sleeping in the last 8 to 10 hours, select "sleeping." If you are coming from work, select "working." If you have had the day "off" from work, select "NON-workday activities." Give a general feel for whether you spent the majority of the previous 8 to 10 hours sleeping, at work, or in Non-workday type activities.

3. **Have you smoked 1 per day?**
Note that the 1 cigarette per day for the past 3 days is not an average. Your consumption must include a minimum of 1 cigarette per day for each day during the past 3 days.

4. **How many cigarettes smoked per day**
Requires a specific number, not a range. Provide the per-day average of the last 3 days.

5. **Usual Brand?**
For the most part, did you smoke your usual brand of cigarettes? If no, give information about the other brand you smoked.

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6. **Indicate changes**
If you answered Question 5 with "no," be sure to select the applicable change from the usual brands in this question. Select "no change" if your smoking habits have not changed. If any other change is selected, you cannot say "no change." If you switched to a lower or higher tar product, specify the product brand name.

7. **Ever smoke other brands?**
Select "Yes" if you sometimes smoked other brands than your usual brand during the last 3 days (e.g., when your usual brand was not available or you were "borrowing" one from someone else).

8. **How many different brands**
Indicate how many different brands you smoked other than your usual brand.

9. **Other brand name**
You will be asked this question for every different brand other than your usual brand that you smoked in the last 3 days. Provide the most complete name possible for the other brand smoked.

10. **Describe the alternate brand**
Select one. You will be asked this question for every different brand other than your usual brand that you smoked in the last 3 days.

11. **Describe the alternate brand**
Select one. You will be asked this question for every different brand other than your usual brand that you smoked in the last 3 days.

12. **Describe the alternate brand**
Select one. You will be asked this question for every different brand other than your usual brand that you smoked in the last 3 days. "Regular" length cigarettes are considered "Kings."

13. **Describe the alternate brand**
Select one. You will be asked this question for every different brand other than your usual brand that you smoked in the last 3 days.

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14. **Describe the alternate brand**
Select one. You will be asked this question for every different brand other than your usual brand that you smoked in the last 3 days.

15. **Number of alternate brand**
You will be asked this question for every different brand other than your usual brand that you smoked in the last 3 days. Do not provide a range. Give your best estimate if you are not sure.

16. **Smoke exposure at work indoors in last 3 days**
You should answer this question only pertaining to jobs you worked at in the last 3 days. If you have been exposed to tobacco smoke at work indoors or in an enclosed space (including during breaks or in the cafeteria), you will be asked to detail the exposure in the following questions. If you have not had exposure to tobacco smoke at work or have worked outdoors only, select "No." If you have not worked in the last 3 days, select "No."

17. **How many jobs with exposure?**
This is not the same as the number of jobs you hold. It refers to the number of jobs at which you have had regular exposure to the tobacco smoke of others in the last 3 days. If you have been exposed to tobacco smoke indoors or in an enclosed space at more than one job in the past 3 days, this next series of questions will be repeated for each job. You should answer this question only pertaining to the last 3 days.

18. **Days exposed at job**
You should answer this question only pertaining to the last 3 days. You will be asked this question for every job at which you have been exposed to the tobacco smoke of others indoors or in an enclosed space in the last 3 days. If the exposure has been continuous through the last 3 days, select all 3 days. "Day 1" refers to the beginning of the last 3 days and "Day 3" refers to yesterday.

19. **Number of hours per day**
You will be asked this question for every job at which you have been regularly exposed to the tobacco smoke of others indoors or in an enclosed space in the last 3 days. Provide a number to the nearest half-hour, not a range.

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20. ***Amount of smoke in work environment***
You will be asked this question for every job at which you have been regularly exposed to the tobacco smoke of others indoors or in an enclosed space in the last 3 days. There is no specific definition for "light," "moderate," or "heavy" exposure. The amount is determined by your perception of the level of exposure.

21. **Have marital type relationship?**
You are to determine whether you perceive any partner as a "marital type relationship." Generally, if you live with someone as a partner, select "Yes."

22. **Spouse smoke exposure in last 3 days**
You should answer this question only pertaining to the last 3 days. If your spouse/partner has smoked in the last 3 days, but did not smoke in your presence or did not smoke at home, select "No."

23. **Products spouse/partner smokes**
Select the product(s) that your spouse/partner has smoked in your presence at home in the last 3 days. You should answer this question only pertaining to the last 3 days. If your spouse/partner has smoked more than one of these products in your presence at home in the past 3 days, select "other" and specify the products smoked. Also select "other" if your spouse/partner has smoked something other than manufactured cigarettes, cigars, cigarillos, or pipes in your presence at home in the last 3 days and then specify the product smoked. If your spouse/partner has smoked one of the products in the last 3 days, but did not smoke it in your presence or did not smoke it at home, do not include it. "Bidi" is a form of cigarette found in India; consists of granulated tobacco rolled in a section of Indian ebony leaf and tied with thread. Also called biri or beedi.

24. **How often**
When calculating the response to this question, think only of your exposure to your spouse/partner's tobacco smoke at home when you were together in the last 3 days.

25. **How many per day**
When calculating the response to this question, think only of your exposure to your spouse/partner's tobacco smoke at home when you were together in the last

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3 days. Give your best estimate to a whole number.

26. **Hours per day**
When calculating the response to this question, think only of your exposure to your spouse/partner's tobacco smoke at home when you were together in the last 3 days. Give your best estimate to the nearest half-hour per day.

27. **Any change in exposure**
When determining the response to this question, think only of changes to your exposure to your spouse/partner's tobacco smoke at home when you were together in the last 3 days. If, for example, your spouse usually smoked at home in your presence but was away on a business trip for 2 days during the last 3, select "Yes" for a change.

28. **Days of change**
When determining the response to this question, think only of changes to your exposure to your spouse/partner's tobacco smoke at home when you were together in the last 3 days. If, for example, your spouse usually smoked at home in your presence but was away on a business trip for 2 days during the last 3, indicate the 2 days of change. "Day 1" refers to the beginning of the 3 days and "Day 3" refers to yesterday.

29. **Kind of change**
When determining the response to this question, think only of changes to your exposure to your spouse/partner's tobacco smoke at home when you were together in the last 3 days. Describe the change that occurred. If, for example, your spouse usually smoked at home in your presence but was away on a business trip for 2 days during the last 3, indicate "away from home, no exposure during that time."

30. **Smoke exposure at home from others in last 3 days**
You should answer this question only pertaining to the last 3 days. If another household member or regular visitor has smoked in the last 3 days, but did not smoke in your presence or did not smoke in your home, select "No."

31. **Number of people**
You should answer this question only pertaining to the last 3 days. Calculate the

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number of household members other than your spouse/partner plus any regular visitors who exposed you to tobacco smoke in your home. If you have been exposed to tobacco smoke from more than one other household member or regular visitor in your home in the past 3 days, this next series of questions will be repeated for each person. Give a single whole number, not a range.

32. **Days exposed from others**
You should answer this question only pertaining to the last 3 days. You will be asked this question for every other household member or regular visitor who smoked in your presence in your home last 3 days. If the exposure has been continuous through the last 3 days, select all 3 days. "Day 1" refers to the beginning of the last 3 days and "Day 3" refers to yesterday.

33. **Products smoked**
Select the product(s) that this other household member or regular visitor has smoked in your presence in your home in the last 3 days. You should answer this question only pertaining to the last 3 days. If this other household member or regular visitor has smoked more than one of these products in your presence in your home in the past 3 days, select "other" and specify the products smoked. Also select "other" if this other household member or regular visitor has smoked something other than manufactured cigarettes, cigars, cigarillos, or pipes in your presence in your home in the last 3 days and then specify the product smoked. If this other household member or regular visitor has smoked one of the products in the last 3 days, but did not smoke it in your presence or did not smoke it in your home, do not include it. "Bidi" is a form of cigarette found in India; consists of granulated tobacco rolled in a section of Indian ebony leaf and tied with thread. Also called biri or beedi. You should think of one household member or regular visitor at a time.

34. **How often**
You will be asked this question for every household member (not including your spouse/partner) or regular visitor who smoked in your presence in your home in the last 3 days. When calculating the response to this question, think only of your exposure to this household member or regular visitor's tobacco smoke in your home when you were together in the last 3 days. You should think of one household member or regular visitor at a time.

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35. **How many per day**
You will be asked this question for every household member (not including your spouse/partner) or regular visitor who smoked in your presence in your home in the last 3 days. When calculating the response to this question, think only of your exposure to this household member or regular visitor's tobacco smoke in your home when you were together in the last 3 days. Give your best estimate to a whole number. You should think of one household member or regular visitor at a time.

36. **Hours per day**
You will be asked this question for every household member (not including your spouse/partner) or regular visitor who smoked in your presence in your home in the last 3 days. When calculating the response to this question, think only of your exposure to this household member or regular visitor's tobacco smoke in your home when you were together. Give your best estimate to the nearest half-hour per day. You should think of one household member or regular visitor at a time.

37. **Smoke exposure in vehicle in last 3 days**
You should answer this question only pertaining to the last 3 days. This question pertains to the smoke of others in enclosed vehicles only.

38. **Number of vehicles**
You should answer this question only pertaining to the last 3 days. Include each vehicle in which you were exposed to the tobacco smoke of others (that is, each car should be counted separately). For example, if you were exposed to the tobacco smoke of others in 2 different cars, truck, and a train in the last 3 days, the total would be "4 different vehicles." If you have been exposed to tobacco smoke of others in more than one vehicle in the past 3 days, this next series of questions will be repeated for each vehicle. Give a single whole number, not a range.

39. **Type of vehicle**
You should answer this question only pertaining to the last 3 days. You will be asked this question for every vehicle in which you were exposed to the tobacco smoke of others in the last 3 days. You should think of one vehicle at a time. For example, if you were exposed to the tobacco smoke of others in 2 cars, a truck, and a train in the last 3 days, this question would be repeated 4 times (in the

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series) and the types of vehicles would be "car, truck, and van" the for the first 3 repeats of these questions and "train" for the fourth repeat.

40. **Days exposed in vehicle**
You should answer this question only pertaining to the last 3 days. You will be asked this question for every vehicle in which you were exposed to the tobacco smoke of others in the last 3 days. If the exposure has been continuous through the last 3 days, select all 3 days. "Day 1" refers to the beginning of the last 3 days and "Day 3" refers to yesterday.

41. **Hours per week**
You should answer this question only pertaining to the last 3 days. You will be asked this question for every vehicle in which you have been exposed to the tobacco smoke of others in the last 3 days. You should think of one vehicle at a time. When calculating the response to this question, think only of your exposure in this vehicle. Give your best estimate to the nearest half-hour per week.

42. **Amount in vehicle**
You should answer this question only pertaining to the last 3 days. You will be asked this question for every vehicle in which you have been exposed to the tobacco smoke of others in the last 3 days. You should think of one vehicle at a time. When determining the response to this question, think only of your exposure in this vehicle. There is no specific definition for "light," "moderate," or "heavy" exposure. The amount is determined by your perception of the level of exposure.

43. **Smoke exposure in other place in last 3 days**
You should answer this question only pertaining to the last 3 days. This question pertains to the tobacco smoke of others in places other than your home, work, or vehicles.

44. **Number of places**
You should answer this question only pertaining to the last 3 days. Calculate the number of different places in which you were exposed to the tobacco smoke of others in the last 3 days. If, for example, you were exposed to tobacco smoke in 2 different bars, count each bar separately. If you have been exposed to tobacco smoke of others in more than one place in the past 3 days, this next series of questions will be repeated for each place. Give a single whole number, not a

APPENDIX E – Interviewer Instructions, Questionnaire, and Weekly Surveys

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range.

45. **Type of place**
You should answer this question only pertaining to the last 3 days. You will be asked this question for every different place in which you were exposed to tobacco smoke of others in the last 3 days. You should think of one place at a time. The name of the specific place is not necessary. Indicate "bar," "restaurant," etc. as appropriate. The same type of place may be repeated for each time this question is repeated for each different specific place, as appropriate. For example, if you were in 2 different bars, you would answer "bar" for the type each time the question was repeated. Be sure to keep the different places clear in your mind as you answer the questions even when the type of place is the same.

46. **Days exposed in place**
You should answer this question only pertaining to the last 3 days. You will be asked this question for every place in which you were exposed to the tobacco smoke of others in the last 3 days. If the exposure has been continuous through the last 3 days, select all 3 days. "Day 1" refers to the beginning of the last 3 days and "Day 3" refers to yesterday.

47. **Hours**
You should answer this question only pertaining to the last 3 days. You will be asked this question for every place in which you have been exposed to tobacco smoke of others in the last 3 days. You should think of one place at a time. When calculating the response to this question, think only of your exposure in this place. Give your best estimate to the nearest half-hour.

48. **Amount in place**
You should answer this question only pertaining to the last 3 days. You will be asked this question for every place in which you have been exposed to tobacco smoke of others in the last 3 days. You should think of one place at a time. When determining the response to this question, think only of your exposure in this place. There is no specific definition for "light," "moderate," or "heavy" exposure. The amount is determined by your perception of the level of exposure.

APPENDIX F - Non-Smoker Exposure Diary and Smoking Diary

Note that these pages represent the pages of the diaries. The diaries are intended to be pocket sized books for the subjects, therefore, the representation here may not be accurate for size.

NON-SMOKER EXPOSURE DIARY
PM Project #1148
Covance Study #12226 8450

VOLUNTEER NUMBER_____

VOLUNTEER INITIALS ___ ___ ___

INSTRUCTIONS FOR NON-SMOKER EXPOSURE DIARY:

- PLACE A CHECK (√) AND ARROW DOWN EVERY TIME ESTIMATED EXPOSURE TO CIGARETTE SMOKE OCCURS.
- *IN THE SAME COLUMN, ESTIMATE THE NUMBER OF* CIGARETTES SMOKED IN YOUR PRESENCE, BY OTHERS.
- RECORD WHERE THE ESTIMATED EXPOSURE TO CIGARETTE SMOKE TOOK PLACE.
- INDICATE THE SMOKE INTENSITY AS: LIGHT (1); MODERATE (2); HEAVY (3).
- USE A PEN.

APPENDIX F –Non-Smoker Exposure Diary and Smoking Diary

Example

TIME	WITH A CHECK (√) INDICATE EXPOSURE/ ESTIMATE # OF CIGARETTES SMOKED BY OTHERS	LOCATION	SMOKE INTENSITY
8:00-8:59 pm	√ - 30	BAR	2
9:00-9:59 pm	↓ - 20	↓	↓
10:00-10:59 pm	√ - 15	BOWLING ALLEY	1
11:00-11:59 pm	√ - 2	CAR	1
12:00-12:59 am	√ - 10	FRIEND'S HOUSE	1

Volunteer Initials ____-____-____ **Volunteer #**_____

Non-smoker Exposure Diary (24-hour period) Date ___/___/___

TIME	WITH A CHECK (√) INDICATE EXPOSURE/ ESTIMATE # OF CIGARETTES SMOKED BY OTHERS	LOCATION	SMOKE INTENSITY
12:00-12:59 am			
1:00-1:59 am			
2:00-2:59 am			
3:00-3:59 am			
4:00-4:59 am			
5:00-5:59 am			
6:00-6:59 am			
7:00-7:59 am			
8:00-8:59 am			
9:00-9:59 am			
10:00-10:59 am			
11:00-11:59 am			

APPENDIX F – Non-Smoker Exposure Diary and Smoking Diary

TIME	WITH A CHECK (√) INDICATE EXPOSURE/ ESTIMATE # OF CIGARETTES SMOKED BY OTHERS	LOCATION	SMOKE INTENSITY
12:00-12:59 pm			
1:00-1:59 pm			
2:00-2:59 pm			
3:00-3:59 pm			
4:00-4:59 pm			
5:00-5:59 pm			
6:00-6:59 pm			
7:00-7:59 pm			
8:00-8:59 pm			
9:00-9:59 pm			
10:00-10:59 pm			
11:00-11:59 pm			

Volunteer Initials ____-____-____ **Volunteer #**_____

Non-smoker Exposure Diary (24-hour period) Date __/__/__

TIME	WITH A CHECK (√) INDICATE EXPOSURE/ ESTIMATE # OF CIGARETTES SMOKED BY OTHERS	LOCATION	SMOKE INTENSITY
12:00-12:59 am			
1:00-1:59 am			
2:00-2:59 am			
3:00-3:59 am			
4:00-4:59 am			
5:00-5:59 am			
6:00-6:59 am			
7:00-7:59 am			
8:00-8:59 am			
9:00-9:59 am			
10:00-10:59 am			
11:00-11:59 am			

APPENDIX F – Non-Smoker Exposure Diary and Smoking Diary

TIME	WITH A CHECK (√) INDICATE EXPOSURE/ ESTIMATE # OF CIGARETTES SMOKED BY OTHERS	LOCATION	SMOKE INTENSITY
12:00-12:59 pm			
1:00-1:59 pm			
2:00-2:59 pm			
3:00-3:59 pm			
4:00-4:59 pm			
5:00-5:59 pm			
6:00-6:59 pm			
7:00-7:59 pm			
8:00-8:59 pm			
9:00-9:59 pm			
10:00-10:59 pm			
11:00-11:59 pm			

Volunteer Initials _____ Volunteer #_____

Non-smoker Exposure Diary (24-hour period) Date __/__/__

TIME	WITH A CHECK (√) INDICATE EXPOSURE/ ESTIMATE # OF CIGARETTES SMOKED BY OTHERS	LOCATION	SMOKE INTENSITY
12:00-12:59 am			
1:00-1:59 am			
2:00-2:59 am			
3:00-3:59 am			
4:00-4:59 am			
5:00-5:59 am			
6:00-6:59 am			
7:00-7:59 am			
8:00-8:59 am			
9:00-9:59 am			
10:00-10:59 am			
11:00-11:59 am			

APPENDIX F – Non-Smoker Exposure Diary and Smoking Diary

TIME	WITH A CHECK (✓) INDICATE EXPOSURE/ ESTIMATE # OF CIGARETTES SMOKED BY OTHERS	LOCATION	SMOKE INTENSITY
12:00-12:59 pm			
1:00-1:59 pm			
2:00-2:59 pm			
3:00-3:59 pm			
4:00-4:59 pm			
5:00-5:59 pm			
6:00-6:59 pm			
7:00-7:59 pm			
8:00-8:59 pm			
9:00-9:59 pm			
10:00-10:59 pm			
11:00-11:59 pm			

Volunteer Initials ___-___-___ Volunteer #_____

Non-smoker Exposure Diary (24-hour period) Date __/__/__

TIME	WITH A CHECK (✓) INDICATE EXPOSURE/ ESTIMATE # OF CIGARETTES SMOKED BY OTHERS	LOCATION	SMOKE INTENSITY
12:00-12:59 am			
1:00-1:59 am			
2:00-2:59 am			
3:00-3:59 am			
4:00-4:59 am			
5:00-5:59 am			
6:00-6:59 am			
7:00-7:59 am			
8:00-8:59 am			
9:00-9:59 am			
10:00-10:59 am			
11:00-11:59 am			

APPENDIX F – Non-Smoker Exposure Diary and Smoking Diary

TIME	WITH A CHECK (√) INDICATE EXPOSURE/ ESTIMATE # OF CIGARETTES SMOKED BY OTHERS	LOCATION	SMOKE INTENSITY
12:00-12:59 pm			
1:00-1:59 pm			
2:00-2:59 pm			
3:00-3:59 pm			
4:00-4:59 pm			
5:00-5:59 pm			
6:00-6:59 pm			
7:00-7:59 pm			
8:00-8:59 pm			
9:00-9:59 pm			
10:00-10:59 pm			
11:00-11:59 pm			

APPENDIX F – Non-Smoker Exposure Diary and Smoking Diary

SMOKING DIARY
PM Project #1148
Covance Study #12226 8450

VOLUNTEER NUMBER_____

VOLUNTEER INITIALS ___ ___ ___

INSTRUCTIONS FOR CIGARETTE DIARY:

- Place a check (√) every time you smoke a cigarette.
- Indicate the location where the cigarette is smoked.
- Save cigarette butts in the container provided.
- Use one sheet per day.
- Use a pen.

APPENDIX F – Non-Smoker Exposure Diary and Smoking Diary

Example

TIME	(√) FOR EACH CIGARETTE SMOKED	LOCATION
8:00-8:59 am	√√√ = 3 cigarettes	1-home;2-car
9:00-9:59 am		
12:00-12:59 pm	√ = 1 cigarette	1-outside
1:00-1:59 pm	√ = 1 cigarette	1-in car
5:00-5:59 pm	√√ = 2 cigarettes	1-outside;1-restaurant
8:00-8:59 pm	√√ = 2 cigarettes	2-bar

Volunteer Initials ____.____.____ **Volunteer #**_____

Cigarette Diary (24-hour period) Date ____/____/____

TIME	(√) FOR EACH CIGARETTE SMOKED	LOCATION
12:00-12:59 am		
1:00-1:59 am		
2:00-2:59 am		
3:00-3:59 am		
4:00-4:59 am		
5:00-5:59 am		
6:00-6:59 am		
7:00-7:59 am		
8:00-8:59 am		
9:00-9:59 am		
10:00-10:59 am		
11:00-11:59 am		

APPENDIX F – Non-Smoker Exposure Diary and Smoking Diary

TIME	(√) FOR EACH CIGARETTE SMOKED	LOCATION
12:00-12:59 pm		
1:00-1:59 pm		
2:00-2:59 pm		
3:00-3:59 pm		
4:00-4:59 pm		
5:00-5:59 pm		
6:00-6:59 pm		
7:00-7:59 pm		
8:00-8:59 pm		
9:00-9:59 pm		
10:00-10:59 pm		
11:00-11:59 pm		

Volunteer Initials ____.____.____ **Volunteer #**_____

Cigarette Diary (24-hour period) Date ____/____/____

TIME	(√) FOR EACH CIGARETTE SMOKED	LOCATION
12:00-12:59 am		
1:00-1:59 am		
2:00-2:59 am		
3:00-3:59 am		
4:00-4:59 am		
5:00-5:59 am		
6:00-6:59 am		
7:00-7:59 am		
8:00-8:59 am		
9:00-9:59 am		
10:00-10:59 am		
11:00-11:59 am		

APPENDIX F – Non-Smoker Exposure Diary and Smoking Diary

TIME	(√) FOR EACH CIGARETTE SMOKED	LOCATION
12:00-12:59 pm		
1:00-1:59 pm		
2:00-2:59 pm		
3:00-3:59 pm		
4:00-4:59 pm		
5:00-5:59 pm		
6:00-6:59 pm		
7:00-7:59 pm		
8:00-8:59 pm		
9:00-9:59 pm		
10:00-10:59 pm		
11:00-11:59 pm		

Volunteer Initials ___.___.___ **Volunteer #**_____

Cigarette Diary (24-hour period) Date ___/___/___

TIME	(√) FOR EACH CIGARETTE SMOKED	LOCATION
12:00-12:59 am		
1:00-1:59 am		
2:00-2:59 am		
3:00-3:59 am		
4:00-4:59 am		
5:00-5:59 am		
6:00-6:59 am		
7:00-7:59 am		
8:00-8:59 am		
9:00-9:59 am		
10:00-10:59 am		
11:00-11:59 am		

APPENDIX F – Non-Smoker Exposure Diary and Smoking Diary

TIME	(√) FOR EACH CIGARETTE SMOKED	LOCATION
12:00-12:59 pm		
1:00-1:59 pm		
2:00-2:59 pm		
3:00-3:59 pm		
4:00-4:59 pm		
5:00-5:59 pm		
6:00-6:59 pm		
7:00-7:59 pm		
8:00-8:59 pm		
9:00-9:59 pm		
10:00-10:59 pm		
11:00-11:59 pm		

Volunteer Initials ____ **Volunteer #**_____

Cigarette Diary (24-hour period) Date __/__/__

TIME	(√) FOR EACH CIGARETTE SMOKED	LOCATION
12:00-12:59 am		
1:00-1:59 am		
2:00-2:59 am		
3:00-3:59 am		
4:00-4:59 am		
5:00-5:59 am		
6:00-6:59 am		
7:00-7:59 am		
8:00-8:59 am		
9:00-9:59 am		
10:00-10:59 am		
11:00-11:59 am		

APPENDIX F – Non-Smoker Exposure Diary and Smoking Diary

TIME	(√) FOR EACH CIGARETTE SMOKED	LOCATION
12:00-12:59 pm		
1:00-1:59 pm		
2:00-2:59 pm		
3:00-3:59 pm		
4:00-4:59 pm		
5:00-5:59 pm		
6:00-6:59 pm		
7:00-7:59 pm		
8:00-8:59 pm		
9:00-9:59 pm		
10:00-10:59 pm		
11:00-11:59 pm		